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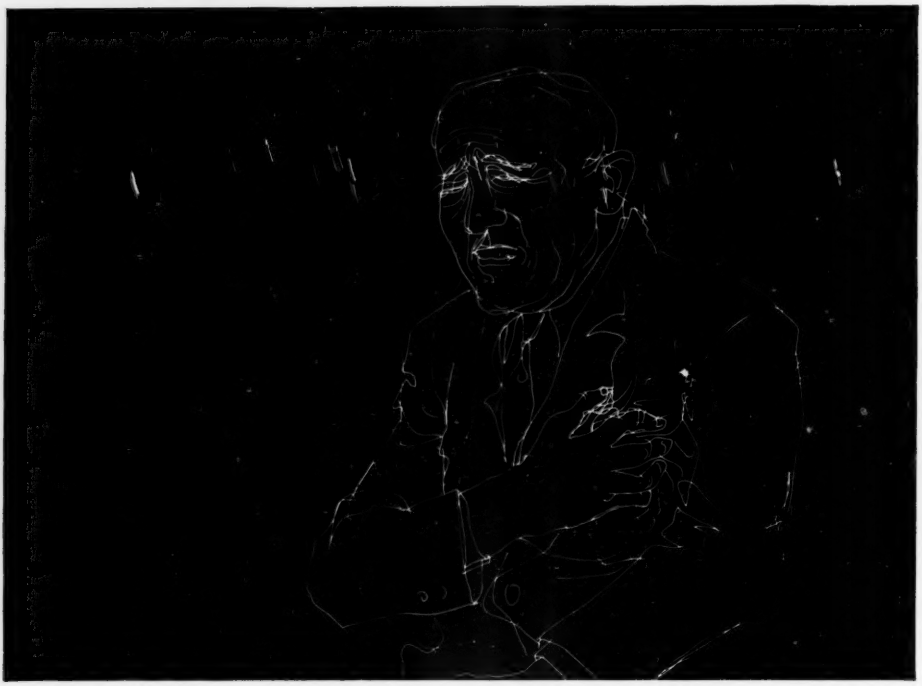

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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953.
2. Humphreys, P., *et al.*: Angiology 3:1 (Feb.) 1952.
3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

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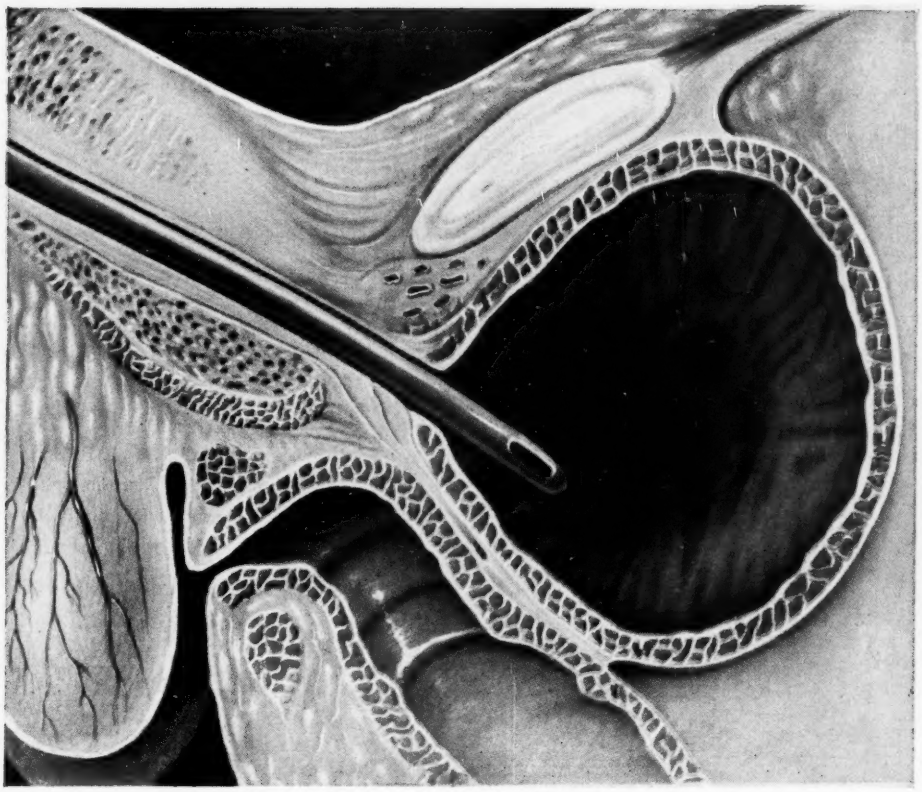

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AUTHORS	No. of Patients	Chronic, Resistant to Other Therapy	TYPES OF ULCERS				RELIEF OF SYMPTOMS (Chiefly Pain)				Surgery or Complications[2]	Side Effects Requiring Discontinuance of Drug[3]	EVIDENCE OF HEALING			
			Duodenal	Jejunal	Stomal	Gastric	Good	Fair	Poor	No Report			Complete	Moderate	None	No Report
Grimson, Lyons, Reeves	100	100	93	7			80	11	4		5		47		19	29
Friedman	15	15	14			1	5		4	6[5]			2			13
Bechgaard, Nielsen, Bang, Gruetlund, Tobiassen	26	26	21			5	16	4	6				8	6	12	
McHardy, Browne, Edwards, Marek, Ward	162		162				136	12	11		3	1	14	9	7	129
Segal, Friedman, Watson	34	34	34[4]				14	13			7	2	5		8	14
Brown, Collins	117	99	117				97	7	8		5	8	55	9	8	40
Asher	77		65		7	5	52	9	16			16		9	21	47
Rodriguez de la Vega, Reyes Diaz	5	4	5				4		1					3	2	
Winkelstein	116	116	102	8		6	102		14				53		18	45
Hall, Hornisher, Weeks	18	18	18				11		1	6[5]			18			
Maier, Meili	38	38	24			14[6]	27	7	4[7]				10	2	5	21
Meyer, Jarman	25	18	25				21		4							25
Poth, Fromm	37	37	37				33	3	1				33	3	1	
Plummer, Burke, Williams	41	41	41				36		5				38		3	
McDonough, O'Neil	104	100	104				63	10	31			11	4		11	89
Broders	60	60	58		1	1	35	19	6				10	1	49[8]	
Legerton, Texter, Ruffin	11		11				11									11
Holoubek, Holoubek, Langford	76	69	76				35	27	10		4	10	26		10	36
Ogborn	42		39	2		1	42[9]									42
Shaiken	48	48	48				33	10	3		2		33	10	3	
Johnston	145	145	145				143		2			2	143		2	
Rossett, Knox, Stephenson	146		141			5	146					4[10]	53			93
TOTALS	*1443*	*968*	*1380*	*17*	*8*	*38*	*1142*	*132*	*131*	*12*	*26*	*54*	*552*	*52*	*179*	*634*
PERCENTAGES		*67.8*	*93.6*	*1.2*	*0.6*	*2.6*	*81.3*	*9.4*	*9.3*			*3.7*	*70.5*	*6.6*	*22.9*	

1. Not included in tabulations.
2. Included in "Relief of Symptoms" as "Poor" and in "Evidence of Healing" as "None."
3. Four had no symptoms when Banthine therapy was begun.
4. Of which seven were penetrative lesions and five partially obstructive.
5. No symptoms were present in four.
6. Two with symptoms only; no demonstrable ulcer.
7. Three were psychopathic patients and one had a ventricular ulcer of the lesser curvature.
8. Roentgen findings after treatment period of two weeks; forty-seven had duodenal deformity.
9. All returned to work within a week.
10. In these four, after relief of symptoms, Banthine was discontinued because of urinary retention.

During the past three years, more than 250 references to Banthine therapy in peptic ulcer and other parasympathotonic conditions have appeared in medical literature. Of these reports, 22 have presented specific facts and figures on the results of treatment in a total of 1,443 peptic ulcer patients, 67.8 per cent of whom were reported as chronic or resistant to other therapy. These results are tabulated above and show:

"Good" relief of symptoms was obtained in 81.3 per cent of the 1,405 patients on whom reports were available.

"Complete" evidence of healing was obtained in 70.5 per cent of the 783 patients on whom reports were available.

In all but 9.3 per cent, relief of pain was "good" or "fair." In all but 22.9 per cent, evidence of healing was "complete" or "moderate."

During treatment, 26 patients required surgery or developed complications other than ulcer which required discontinuance of the drug before results could be evaluated.

Of the remaining 1,417 patients, only 3.7 per cent experienced side effects sufficiently annoying to require discontinuance of the drug.

*Volume containing complete references, with abstracts of 39 additional reports, will be furnished on request by

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VOLUME 93 MARCH 1954 NUMBER 3

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CENTRAL NERVOUS SYSTEM INVOLVEMENT IN DISORDERS OF COLLAGEN

BERNARD I. LEWIS, M.D., F.R.C.P. (C)
DAVID W. SINTON, M.D.
AND
JOHN R. KNOTT, Ph.D.
IOWA CITY, IOWA

SINCE the introduction of the term "collagen diseases," [1] the concept of an intimate relationship between these apparently disparate disorders has been the subject of considerable interest and controversy. One of the characteristic features of these syndromes is the involvement of multiple body systems, but, thus far, the frequency and importance of central nervous system (CNS) manifestations have not been accorded proper recognition. Neuropathologic lesions have been reported sporadically in disseminated lupus erythematosus * and polyarteritis nodosa,† but the commoner, "rheumatic" members of this group have been virtually ignored.

Interest in this aspect of these disorders was stimulated during a recent study [8] by the unexpected, and heretofore unreported, finding of significant, although subclinical, mental deficit in certain patients with rheumatoid arthritis. No basis for this intellectual impairment could be detected, other than the arthritic process itself. These patients exhibited no overt neurologic abnormalities.

A subsequent survey of the literature provided additional information, which strengthened our suspicion that the CNS is affected much more frequently than has been generally appreciated. Bauer and his co-workers ‡ detected neurologic and cerebrospinal fluid (CSF) abnormalities in their patients with rheumatoid arthritis. They did not elaborate, however, upon the nature or significance of these changes. Freund [11] described what he considered to be characteristic perineuritic rheumatoid nodules. Bruetsch [12] found a high incidence of "rheumatic obliterating arteritis" of the CNS during his postmortem studies on psychotic persons with rheumatic heart disease. Similar changes were noted by Kernohan and co-workers [13] in their cases of rheumatic endocarditis. Lam and Tyler [14] obtained abnormal EEG's from a high proportion of their rheumatic fever patients. These electrophysiologic aberrations could not be related to the presence of chorea or overt neurologic findings and were interpreted to indicate diffuse cerebral involvement.

This investigation was supported by a grant from the Central Scientific Research Fund, College of Medicine, State University of Iowa.

From the Departments of Medicine (Dr. Lewis and Dr. Sinton) and Psychiatry (Dr. Knott), College of Medicine, State University of Iowa.

* References 2, 3, and 4.

† References 5, 6, and 7.

‡ References 9 and 10.

The current investigation was undertaken to pursue further the foregoing observations of mental deficit in patients with rheumatoid arthritis and to determine the incidence and nature of CNS abnormalities in these "diseases of collagen," with particular reference to the commoner members of the group. Three specific investigative procedures were used to detect nervous system involvement. These were electroencephalography (EEG), cerebrospinal fluid (CSF) analysis, and a special psychometric test, the Vocabulary-Kohs Index (VKI).

1. *Electroencephalography.*—Routine EEG's were recorded and interpreted by one of us (J. R. K.) who had no other contact with the patients. These were 15 lead records, with the electrodes placed bilaterally over the occipital, parietal (association), motor, frontal, anterior temporal, and posterior temporal areas, and there were independent electrodes on the ear lobe and a vertex reference electrode. Scalp-ear reference (monopolar), scalp-vertex reference, and scalp-scalp reference (bipolar) recordings were made. Recording was carried out with the patient awake and eyes closed. Minimum record length was 25 minutes. The tracings were classified on the Gibbs scale,[15] with the variation in the EEG in the "normal" population secured from the data of Gibbs, Gibbs, and Lennox [15] on a control group of 1,000 neurologically screened young adults.

2. *Cerebrospinal Fluid Analysis.*—CSF was obtained by routine lumbar puncture technique. Cell counts were performed immediately. Ten cells or more per cubic millimeter was considered abnormal. Quantitative protein estimations were performed in the Biochemistry Laboratory of our University Hospitals, with levels between 40 and 49 mg. per 100 ml. graded borderline and those 50 mg. per 100 ml. or higher considered definitely abnormal. Colloidal gold tests were performed in our Central Laboratory, with curves having a maximal rise to 3 considered borderline and rises exceeding this classed as definitely abnormal.

3. *Vocabulary-Kohs Index.*—This simple psychometic test is a sensitive indicator of impairment of intellectual function. It provides an objective measurement of the degree of mental deficit and has been validated clinically and statistically in toxic mental states,[16] neurosyphilis,[17] and schizophrenia.[18] The details of the procedure are available in the reference articles and will not be reviewed here. It will suffice to note that the two subdivisions of the test are each scored as years of mental age, with the final index (VKI) being the age disparity between these two scores. Although it has been reported [18] that disparities of two years are strongly suggestive of mental deficit, on the basis of subsequent investigation [17] VKI's of 2 to 2.9 years were considered borderline and only those of 3 years or more were graded as definitely abnormal in this study. This psychometric procedure, although capable of detecting mental deficit of subclinical degree, does not identify the underlying pathologic process. Neither is it capable of differentiating between transient functional disturbances and permanent organic changes or between focal and diffuse CNS damage. As will be discussed later, it is probable that a diffuse cortical pathologic process is required to make a VKI abnormal. All the psychometric determinations were performed by one clinical psychologist,§ in the Psychometric Clinic of our University Hospitals.

§ Miss Margaret Shuttleworth, Ph.D., Clinical Psychologist, University Hospitals.

This report ‖ will present the findings in a group of 51 subjects selected from the public and private services of our University Hospitals. Before admission to the study, each subject was carefully screened for any past or present evidence of CNS trauma and/or disease. To secure as "pure" data as possible, we excluded potential subjects who demonstrated "contaminating" processes such as cardiac decompensation, uremia, significant pyrexia, and senescence, which might, in themselves, alter CNS function and distort the test results. For similar reasons, lumbar puncture was always the last test procedure to be performed. Each subject was carefully examined (history, physical examination, detailed neurologic survey,¶ and indicated laboratory tests) and then subjected to the special investigative procedures prior to the institution of specific therapy, with particular reference to corticotropin (ACTH) and cortisone.

RESULTS

Rheumatoid Arthritis (Table 1).—All 13 subjects demonstrated clinical and laboratory evidence of mild to moderate activity of their arthritis. Four had "early" arthritis (duration less than one year) and the remainder had "late" arthritis (duration three or more years). Spondylitis was unequivocally present in two subjects, with questionable changes in three others. Abnormal EEG's were obtained from seven subjects, with evidence of focal activity in three. CSF abnormalities were present in four subjects, two of whom had only borderline changes. Lumbar puncture was not performed in one subject, who was prematurely discharged from hospital. Quantitatively, the spinal fluid protein changes did not parallel those of the plasma proteins. Seven subjects had abnormal VKI's, although three were in the borderline range. There were no significant clinical neurologic findings.

Disseminated Lupus Erythematosus (Table 2).—These 11 subjects demonstrated "early" active processes. The duration of overt manifestations ranged from 1 to 10 months. Confirmatory skin biopsies were obtained in each case, and L. E. cells were present (bone marrow and/or peripheral blood) in seven subjects on one or more occasions. An apparently false positive serologic test for syphilis was found in only one subject. Nine had abnormal EEG's, with focal activity noted in four tracings. Seven had abnormal CSF findings, but two were borderline. Spinal fluid and plasma protein abnormalities could not be correlated. Psychometric tests were performed by 8 of the 11 subjects, and, except for one borderline score, all results were normal. Results of clinical neurologic examination were completely normal for six subjects. Of the remainder, one (normal EEG) had generalized hypoactivity of all deep tendon reflexes; another (normal EEG) demonstrated a recurrent bilateral ptosis, triceps weakness, and weakness of dorsiflexion with unsustained ankle clonus of the right foot; a third (abnormal EEG) had a fine nystagmus, peripheral paresthesias, and hyperactive deep tendon reflexes; a fourth (abnormal EEG) revealed moderate muscular atrophy, weakness, and tenderness of both

‖ A preliminary report has appeared, in abstract form, in the Proceedings of the 45th Annual Meeting of the American Society for Clinical Investigation, Atlantic City, N. J., May 4, 1953.[19]

¶ Dr. A. D. Sahs, Professor of Neurology, and his staff reviewed all questionable cases.

RHEUMATOID ARTHRITIS

CASE NO.	SEX	AGE	STAGE OF DISEASE[1]	SPONDYLITIS[2]	ESR[3]	PLASMA PROTEINS[4]	SPECIFIC TEST RESULTS[5]		
							EEG	CSF	VKI
1	M	36	L	A	86	3.4/3.1	+	0	0
2	F	17	E	A	112	—	+Focal	0	0
3	F	34	L	A	92	—	+	0	±
4	F	35	E	Q	114	4.1/2.1	+Focal	0	0
5	M	58	L	P	86	5.0/4.0	0	+	±
6	F	42	L	A	96	—	+	±	+
7	M	44	L	A	96	4.0/3.5	0	0	+
8	F	28	L	A	63	3.6/4.1	+	0	+
9	F	40	L	Q	46	4.3/2.9	+Focal	0	0
10	F	35	E	Q	40	4.2/2.1	0	±	0
11	F	36	E	A	78	3.7/3.6	0	+	±
12	M	25	L	P	60	4.1/5.0	0	−	0
13	M	20	L	A	48	4.5/2.4	0	0	+

1. E=Early; L=Late (See text)
2. A=Absent; P=Present; Q=Questionable
3. Erythrocyte Sedimentation Rate in mm./hr. (Westergren Method)
4. Albumin/Globulin in gms./100ml.
5. +=Abnormal; ±=Borderline; 0=Normal; —=Not performed

Table 1

DISSEMINATED LUPUS ERYTHEMATOSIS

CASE NO.	SEX	AGE	ESR[1]	PLASMA PROTEINS[2]	"L.E." CELLS[3]	SPECIFIC TEST RESULTS[4]		
						EEG	CSF	VKI
14	F	45	121	3.2/3.4	P	+Focal	+	−
15	F	16	47	3.8/4.1	A	+Focal	0	0
16	F	32	—	5.3/2.6	A	0	±	0
17	M	21	69	3.4/2.9	P	+	0	0
18	M	32	88	4.4/3.7	P	+	+	0
19	M	58	51	4.4/3.0	P	+	+	±
20	F	24	94	4.1/3.2	P	0	0	−
21	F	29	79	4.4/3.2	P	+	+	0
22	F	16	99	4.2/4.1	A	+	+	0
23	F	40	14	5.0/2.4	A	+Focal	±	−
24	F	28	104	1.8/4.6	P	+Focal	0	0

1. Erythrocyte Sedimentation Rate in mm./hr. (Westergren Method)
2. Albumin/Globulin in gms./100ml.
3. A=Absent; P=Present
4. +=Abnormal; ±=Borderline; 0=Normal; —=Not performed

Table 2

upper extremities, with roentgenographic evidence of an atypical polyarthritis, and a fifth subject (abnormal EEG) exhibited recurring convulsive seizures, both generalized and Jacksonian in type, with evidence of bilateral pyramidal tract involvement.

Acute Rheumatic Fever (Table 3).—This group contained 10 subjects in their initial attacks of rheumatic fever. All were studied within a period of 2 to 8 weeks of the onset of their illness except for one subject, who was not seen until the fifth month of his disease. There was evidence of both arthritis and carditis in each case. The EEG's were abnormal for six subjects. The resting record was normal in a seventh subject, but the posthyperventilation tracing was abnormal, and this EEG

ACUTE RHEUMATIC FEVER

CASE NO.	SEX	AGE	ESR[1]	PLASMA PROTEINS[2]	SPECIFIC TEST RESULTS[3]		
					EEG	CSF	VKI
25	M	17	28	40/30	0	0	0
26	M	16	92	44/34	+	0	0
27	M	17	35	50/37	±	0	+
28	M	16	68	48/24	+	±	0
29	M	11	62	8.1 (Total)	+ Focal	±	0
30	M	16	60	3.7/1.7	+ Focal	+	0
31	M	35	51	—	0	+	+
32	M	17	103	42/3.0	+ Focal	±	0
33	F	15	112	3.4/3.8	+ Focal	+	0
34	F	44	11	—	0	±	±

1 Erythrocyte Sedimentation Rate in mm/hr (Westergren Method)
2 Albumin/Globulin in gms/100 ml
3 +=Abnormal; ±=Borderline; 0=Normal; —= Not performed

Table 3

was graded borderline. Four EEG's disclosed abnormal focal activity. CSF abnormalities were present in seven subjects, but four were borderline. The CSF protein changes did not reflect those of the plasma proteins. There were three abnormal VKI's, one of which was borderline. Neurologic findings were not remarkable.

Rheumatic Heart Disease (Table 4).—(*a*) Active: These were five subjects with active rheumatic valvulitis who had had one or more recognized episodes of rheumatic fever in the past. Their initial attacks antedated the current exacerbation by 3 to 14 years. All were studied within 2 to 8 weeks of the onset of their present episode. Three displayed abnormal EEG's without evidence of focal activity (one of these subjects revealed significant focal dysrhythmia on a follow-up EEG two months later, when, by all other criteria, her disease was clinically inactive). Borderline CSF changes were noted in one instance, and the VKI's were entirely normal. There were no significant neurologic findings.

RHEUMATIC HEART DISEASE

A. Active*

CASE NO.	SEX	AGE	ESR[1]	PLASMA PROTEINS[2]	SPECIFIC TEST RESULTS[3]		
					EEG	CSF	VKI
35	M	17	87	—	0	±	0
36	M	17	39	3.8/2.4	+	0	0
37	F	19	119	4.1/2.4	+	0	0
38	F	22	50	4.8/2.4	0	0	0
39	F	19	37	5.3/3.0	+	0	0

B. Inactive*

40	M	27	3	—	0	+*	0
41	F	34	75*	4.5/3.2	0	0	0
42	F	26	14	4.2/3.2	0	0	±
43	M	22	10	4.4/2.5	0	±	±

* See text
1 Erythrocyte Sedimentation Rate in mm/hr. (Westergren Method)
2 Albumin/Globulin in gms./100ml
3 +=Abnormal; ±=Borderline; 0=Normal; —=Not performed

Table 4

DERMATOMYOSITIS

CASE NO.	SEX	AGE	ESR[1]	PLASMA PROTEINS[2]	SPECIFIC TEST RESULTS[3]		
					EES	CSF	VKI
44	M	49	70	3.7/3.9	0	0	0
45	F	45	94	2.8/2.9	0	0	0
46	F	28	6	4.6/2.9	+	+	0
47	F	28	12	3.8/2.3	+ Focal	0	0
48	F	27	40	3.7/2.4	0	0	0

ACUTE GLOMERULONEPHRITIS

49	M	17	55	4.7/4.1	+	0	— Blind
50	F	28	33	3.6/2.7	0	0	0
51	F	28	85	4.4/4.1	+ Focal	-	0

1. Erythrocyte Sedimentation Rate in mm./hr. (Westergren Method)
2. Albumin/Globulin in gms./100ml
3. +=Abnormal; ±=Borderline; 0=Normal; —=Not performed

Table 5

(*b*) Inactive: These were four subjects with chronic rheumatic heart disease of six or more years' duration. Each demonstrated the classical findings of mitral stenosis. In one instance there was a coexistent aortic valvular lesion. In none had activity of the rheumatic process been evidenced within at least the previous 12 months. The increased sedimentation rate (ESR) in one subject was related to an intercurrent cystitis. These subjects provided no EEG abnormalities. One grossly abnormal CSF was found and was sufficiently different in character and degree from all others in this study as to suggest either a laboratory error or the coexistence of another disease. We could find no evidence of an additional pathologic process and, unfortunately, were not able to repeat the lumbar puncture prior to discharge. Borderline CSF changes were noted in a second subject, and there were two borderline VKI's. The neurologic examinations were completely unrevealing.

Dermatomyositis (Table 5).—These five subjects presented characteristic pictures of this uncommon disorder. Each had overt manifestations of less than six months' duration and exhibited clinical evidence of moderate activity of the disease despite a normal ESR in two subjects. Biopsy findings were consistent with this diagnosis in each case. Two subjects had abnormal EEG's, with one demonstrating marked focal activity. One subject had CSF abnormalities, and another had a borderline VKI. Clinical neurologic changes were minimal and nonspecific. They consisted essentially of muscular tenderness, weakness, and wasting; variable hyporeflexia, and cutaneous evidence of vasomotor dysfunction.

Glomerulonephritis (Table 5).—These were three subjects in their initial episodes of acute nephritis. At the time of testing all three were virtually asymptomatic but each manifested laboratory evidence of activity (increased ESR's, proteinuria, and abnormal urinary sediments). None was febrile, azotemic, or hypertensive at the time of testing. Two subjects had abnormal EEG's, with one of these revealing focal activity. The CSF analyses were normal in the two subjects thus examined. Two subjects were tested psychometrically, and each obtained a normal VKI. There were no significant findings on neurologic examination.

OBSERVATIONS AFTER THERAPY

Eight subjects (Table 6) had received corticotropin and/or cortisone; one, with disseminated lupus, was treated with quinacrine (Atabrine), and two, one with acute rheumatic fever and another with active rheumatic heart disease, had been on salicylates alone. These 11 subjects were retested, completely or partially, approximately two to three weeks after cessation of therapy. Comparison of their pretreatment and post-treatment test results disclosed variable and inconclusive findings. After treatment the results were improved in four subjects, essentially unchanged in five, and worse in the remaining two. Two abnormal EEG's (one with focal changes) reverted to normal; three abnormal EEG's (one with focal changes) were again abnormal (focal changes now present in two), and three normal EEG's remained unchanged. One abnormal CSF became borderline; two normal CSF's became borderline, and three normal CSF's remained unchanged. Two abnormal VKI's (one borderline) reverted to normal, and a third became borderline; one normal VKI became borderline, and one abnormal VKI was unchanged.

Clinically, all these subjects improved with therapy, with one exception. This was a young woman with dermatomyositis (pretreatment results completely normal) who developed a manic psychosis while receiving corticotropin, which required electroshock therapy for resolution. Her only repeat test (CSF) revealed borderline abnormalities. The disparity between the over-all clinical improvement and the post-treatment test results suggests that the related CNS changes are not merely the physiologic reflections of a general state of toxicity. As the discussion to follow will indicate, it is more likely that organic neurovascular lesions underlie these abnormal CNS findings.

OBSERVATIONS AFTER THERAPY

CASE NO.	DIAGNOSIS	TREATMENT	CLINICAL EFFECT	SPECIFIC TEST RESULTS [1]					
				Pre Therapy			Post Therapy		
				EEG	CSF	VKI	EEG	CSF	VKI
5	Rheumatoid Arthritis	ACTH	Improved	0	+	±	0	±	0
6	Rheumatoid Arthritis	ACTH	Improved	+	±	+	+	−	+
7	Rheumatoid Arthritis	ACTH + Cortisone	Improved	0	0	+	0	0	±
20	Disseminated Lupus	ACTH	Improved	0	0	−	−	0	−
23	Disseminated Lupus	Atabrine	Improved	+ Focal	±	−	+ Focal	−	−
27	Acute Rheumatic Fever	ACTH	Improved	±	0	+	−	−	0
33	Acute Rheumatic Fever	Salicylates	Improved	+ Focal	+	0	0	−	−
37	Active Rheumatic Heart Disease	Salicylates	Improved	+	0	0	+ Focal	−	−
44	Dermatomyositis	ACTH	Improved	0	0	0	0	±	±
48	Dermatomyositis	ACTH + Cortisone	Manic Psychosis	0	0	0	−	±	−
49	Acute Glomerulonephritis	Cortisone	Improved	+	0	− Blind	0	0	− Blind

1. +=Abnormal; ±=Borderline; 0=Normal; −=Not performed

Table 6

Thirteen additional subjects were given corticotropin and/or cortisone but could not be retested for various reasons. Nine evidenced significant clinical improvement; one exhibited little if any change, and three deteriorated and died during treatment. One of the latter was a young girl with disseminated lupus whose condition pursued a fulminating course and who manifested terminal convulsions with hemiplegia, lapsed into coma, and died. Her EEG had been abnormal, with marked focal activity. Deterioration was so rapid in this case that retesting was impossible, and, unfortunately, permission for autopsy was refused. The remaining two subjects had dermatomyositis. One followed a progressive downhill course with terminal neurologic complications almost identical with those of the subject with disseminated lupus mentioned above. She, also, had demonstrated an abnormal EEG with focal changes. The other had completely normal test results and gradually deteriorated, despite

hormonal therapy, with her immediate causes of death being hypostatic pneumonia and septicemia. Postmortem examinations were performed in both cases, but, in each, permission to examine the CNS was refused.

COMMENT

Forty-two of these subjects (82%) were found to have one or more abnormal results to their specific test procedures (Table 7). In 2 instances all three results were abnormal; 19 subjects each had two abnormal findings, and 21 had single abnormalities.

SPECIFIC TEST RESULTS
TOTALS

Incidence of Test Abnormalities Per *Disease*

DIAGNOSIS		NO. OF SUBJECTS	EEG		CSF		VKI	
			No. Abnormal	No. Focal	No. Abnormal	No. Borderline	No. Abnormal	No. Borderline
Rheumatoid Arthritis		13	7	3	2	2	4	3
Disseminated Lupus		11	9	4	5	2	0	1
Acute Rheumatic Fever		10	7*	4	3	4	2	1
Rheumatic Heart Disease	Active	5	3	0	0	1	0	0
	Inactive	4	0	0	1	1	0	2
Dermatomyositis		5	2	1	1	0	0	0
Acute Glomerulonephritis		3	2	1	0	0	0	0
Total		*51*	*30**	*13*	*12*	*10*	*6*	*7*

Incidence of Test Abnormalities Per *Subject*

3	2	1	0
1	4	7	1
1	5	4	1
0	8	1	1
0	0	4	1
0	1	2	1
0	1	1	3
0	0	2	1
2	*19*	*21*	*9*

*One of these abnormal EEGs was in the borderline range (See text)

Table 7

Thirty subjects (59%) had abnormal EEG's (one borderline), and 13 of these records (43%) revealed marked focal dysrhythmia. Twenty-two subjects (43%) had CSF abnormalities (10 borderline) which related only to the protein content and colloidal gold curve, as has been previously reported in rheumatoid arthritis.[10] There were no pathologic findings in the cell counts, chloride and sugar concentrations, or complement-fixation reactions for syphilis. Thirteen subjects (25%) had abnormal VKI's (7 borderline).

This incidence of central nervous system dysfunction, as determined by these electrophysiologic, biochemical, and psychometric indices, is impressively high and has no apparent basis other than the particular collagen disorder present. The obvious questions which arise pertain to the significance of these abnormalities.

Are they indicative of transient, physiologic CNS derangement or permanent organic damage—and what is the effect of the neurologic process, both immediate and long term, on the patient and on his disease?

Although our data do not provide simple, direct answers to these questions, they do permit certain inferences to be drawn. The incidence of EEG abnormalities, in itself, supplies no differential information, but the large number of records with focal dysrhythmia, and many others with abnormal slow activity commonly demonstrating some disparity between the two sides, strongly suggest the presence of organic brain disease. This coincides with the findings and interpretations of other investigators in studies on disseminated lupus [3] and rheumatic fever.[14] The cerebrovascular accidents, convulsive seizures, and other neurologic phenomena noted in subjects with disseminated lupus and the common occurrence of chorea in rheumatic fever offer more tangible confirmation of organic brain damage in these syndromes. The clinical course of the subject with dermatomyositis who demonstrated a focal type EEG record and subsequently exhibited convulsive seizures and hemiplegia testifies that organic CNS lesions occur in this disorder as well.

The significance of the CSF changes is more questionable. Their lack of quantitative correlation with those of the plasma proteins favors an independent pathologic origin in the CNS. Qualitative electrophoretic studies may settle this question, but certain technical difficulties must be overcome before the small amount of CSF usually available can be accurately analyzed. The presence of a distinct correlation between the CSF and EEG findings (15 of the 30 subjects with abnormal EEG's also had CSF changes) provides further evidence in favor of a common pathologic denominator in the CNS. These combined abnormalities were most prevalent in the subjects with disseminated lupus, rheumatic fever, and rheumatoid arthritis.

Previous studies # have indicated that diffuse cortical involvement is probably required to produce an abnormal VKI. In view of the tendency toward a patchy distribution of the vascular lesions in these collagen disorders, the relatively low incidence (25%) of psychometric abnormalities might thus have been anticipated. Supportive evidence is provided by Glaser's [7] recent neuropathologic study which revealed that, in disseminated lupus at least, there may be either a focal or diffuse encephalomalacia. He found these lesions to be secondary to a specific endarteritis characterized by the fibrinoid degenerative changes originally described by Klemperer.[20] Glaser noted also that, despite extensive cerebral lesions, neurologic signs and symptoms were often absent.

The histopathologic findings of Bruetsch [12] and Kernohan and co-workers [13] are equally pertinent and contribute further to an understanding of our results. Bruetsch, during postmortem studies on mental hospital patients with rheumatic heart disease, was impressed by the frequent occurrence of "rheumatic" endarteritic CNS lesions. Although gross infarcts were often present, he noted a predilection for the small cortical and meningeal vessels, with resultant microscopic areas of degeneration and softening. Twenty-three of Kernohan's 42 patients with rheumatic endocarditis came to autopsy, and 22 demonstrated similar miliary foci of degeneration in the cortex and basal ganglia, which were interpreted as minute infarcts. Twenty-one of these 23 patients had neuropsychiatric disorders, 5 of which were psychoses. Many were in an acute or subacute exacerbation of their rheumatic endocarditis at the time of

References 16, 17, and 18.

death. The vast majority (85%) of Bruetsch's group were also considered to be in an active, although often subclinical, rheumatic state. Bruetsch suggests that these pathologic lesions may underlie many of the intellectual and emotional aberrations which subsequently arise in rheumatic patients. He believes that variable behavior disorders and mental deficit states may thus result in childhood and, on the same basis, that there may develop psychopathologic pictures resembling schizophrenia in the young adult and involutional psychosis in middle and later life.

The morphologic data presented in these pathologic studies, if applicable to our subjects, importantly elucidate the nature of our findings and strongly favor the existence of organic brain damage. Glaser's comments on the frequent lack of clinical and pathologic correlation help to explain the apparent discrepancy between our plethora of test abnormalities and relative paucity of clinical neurologic signs. This peculiar paradox may also be related to the seeming predilection, in our series, for overt neurovascular complications to develop only in subjects with disseminated lupus and dermatomyositis. It is well known, however, and has been emphasized in a recent review by Ehrich,[21] that these various disorders of collagen have a partiality for vessels of certain caliber (and possibly, for certain anatomical sites).

In reply to our initial question, therefore, the evidence presented weighs heavily in the direction of organic brain damage rather than transient physiologic disturbance as the basis for our high incidence of CNS dysfunction. However, these are not mutually exclusive and, in all likelihood, frequently coexist.

Our second question was concerned with the possible effects of this neuropathologic process on the patient and his disease. That serious immediate sequelae can result is exemplified by the acute neurologic phenomena which may complicate disseminated lupus and dermatomyositis and the choreiform syndromes which commonly attend rheumatic fever. On more speculative footing is the possibility that states of autonomic and/or endocrine dysfunction may be initiated which, in their turn, impair the body protective mechanisms and, perhaps, enhance the course of the primary disease. It is common knowledge that patients with these syndromes frequently exhibit vasomotor and other phenomena indicative of autonomic imbalance, and often respond dramatically, albeit temporarily, to hormonal therapy. Further research will be required to elucidate these potentially important but conjectural considerations.

The long-term consequences are rather more difficult to evaluate. The incidence of abnormal test results in our arthritic subjects with illnesses of many years' duration supports the concept of continued and/or recurring CNS disease. Investigators in the psychosomatic field have commented * on the personality configuration and emotional instability of patients with rheumatoid arthritis and have proposed that psychopathologic factors may play an etiologic role in this disorder. Our findings tend to suggest, conversely, that the psychic features may be a result of, rather than a causal factor in, this particular syndrome. Bruetsch's beliefs (see above) that various behavior disorders, deficit states, and psychotic reactions probably eventuate from a "rheumatic encephalitis" are germane here and merit further investigation.

The parallel between certain aspects of the collagen disorders and another pansystemic disease, syphilis, deserves brief comment. The incidence of each is relatively

* References 22 and 23.

high, yet evidence of a primary, initiating process is often absent. Their pathogenetic common denominator can be regarded as an obliterative endarteritis of patchy but wide distribution. In syphilis there is early spirochetal involvement of the CNS, but acute syphilitic meningitis and the late cerebrovascular and parenchymatous sequelae develop in but a small proportion of cases. Major and minor variations on this general theme appear to be present in the collagen syndromes as well. Furthermore, the characteristic coexistence of cardiovascular syphilis and neurosyphilis suggests that this combination of pathologic events may also occur in some of the collagen disorders, with the CNS component having been relatively ignored thus far in favor of the more striking visceral changes.

SUMMARY

Fifty-one carefully screened subjects with representative collagen disorders were studied with particular reference to central nervous system (CNS) involvement. Electroencephalography (EEG), cerebrospinal fluid (CSF) analysis, and a special psychometric test, the Vocabulary-Kohs Index (VKI), were the specific procedures used for the detection and evaluation of nervous system derangement.

Forty-two subjects (82%) demonstrated abnormal CNS findings. These included in particular, 12 of 13 subjects with rheumatoid arthritis, 10 of 11 with disseminated lupus, and 9 of 10 with acute rheumatic fever. Thirty subjects (59%) had abnormal EEG records, 13 of which revealed marked focal dysrhythmia. Twenty-two subjects (43%) presented CSF changes characterized by abnormal protein contents and/or colloidal gold curves. Thirteen subjects (25%) achieved VKI's indicative of mental deficit.

Twenty-four subjects were observed during and after therapy consisting of corticotropin (ACTH) and/or cortisone (in all but 3 cases). Eleven were retested, completely or partially, two to three weeks after treatment, with inconclusive results; viz., the test findings were improved in 4 subjects, worse in 2, and unchanged in the other 5. Two subjects (one with dermatomyositis and the other with disseminated lupus) developed serious neurologic complications during hormonal therapy which contributed directly to their death. Both had abnormal pretreatment EEG's, with marked focal dysrhythmia.

The significance of this high incidence of CNS derangement is discussed in relation to the nature and consequences, immediate and long-term, of the basic pathologic process. Evidence is presented which testifies strongly to the presence of organic brain damage (rather than transient physiologic dysfunction) as the substratum of our abnormal test results.

Clinical and histopathologic correlations are offered to explain the seeming disparity between the many test abnormalities and few overt neurologic signs; to support the tentative concept that secondary states of autonomic and/or endocrine imbalance may be initiated which, in turn, adversely affect the body economy and enhance the course of the primary disease process, and to endorse the thesis that intellectual, behavioral, and emotional aberrations may ultimately develop as distant sequelae of the fundamental neurovascular lesions.

A parallel is drawn between the course and certain characteristics of these disorders and syphilis in further, albeit conjectural, elucidation of the nature and prevalence of CNS involvement in the "diseases of collagen."

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STUDIES ON SERUM CHOLESTEROL AND OTHER CHARACTERISTICS OF CLINICALLY HEALTHY MEN IN NAPLES

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IN THE control of the concentration of blood cholesterol the diet clearly has a marked and ubiquitous effect, but the picture differs in various species. Man does not compare with the rabbit and the chick in sensitivity to exogenous cholesterol, but his response to total fats in the diet appears to be greater.* Obviously, quantitative information on the effect of the diet on the blood cholesterol level in man must be sought from man himself.

Experiments on this problem in man generally have several defects. The studies reported so far have largely ignored the important factor of age [7] and have been limited to a few weeks or months of drastic change from previous lifelong subsistence on the relatively high-fat diet that is almost universally used in the United States at the present time.

The present paper reports findings on clinically healthy men in Naples, where the habitual diet, like that of the average for Italy as a whole, provides only about 20% of total calories from all fats as contrasted with some 40% in the United States. The relationship between blood cholesterol and relative obesity, as well as age, was examined. Finally, because a major interest in the cholesterol problem in man is in connection with coronary and related degenerative heart disease, explorations were also made on the electrocardiographic characteristics of the Italian subjects as compared with American controls.

Dr. Keys was a Senior Fulbright Fellow (Research) during the time when the data were collected in Naples.

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* References 1-6.

SUBJECTS

The Neapolitan subjects were regular members of the city fire department and men employed as *vigili annonari.* It was considered that between them they might be reasonably representative of the general population of lower class Neapolitans exclusive of men in strictly sedentary jobs and of men engaged in very strenuous manual labor. On medical examination a few subjects were rejected as being not completely clinically healthy. There remained 83 subjects, including 4 men with moderately elevated blood pressures in the nonbasal state but without other evidence of hypertensive disease.

The firemen in Naples are more like a military organization than their American counterparts. They enlist in the service and live continuously in barracks for the first three years. Thereafter, they spend alternate 24-hour periods in the barracks, so they receive half of their meals from the fire department. A good deal of their time is spent in removing hazards to safety, loose stucco and stone on buildings, etc. Fires are rare, but the equipment is maintained and tested frequently. Besides all this, they have a regular program of drill and physical exercise.

TABLE 1.—*Dietary Comparisons of Italy and the United States and of Naples and Minnesota**

	Italy	U. S.	Naples	Minnesota
Calories	2,340	3,130	3,010	2,980
Proteins, gm.	75	90	97	92
Proteins, % of all Calories	13	12	13	12
Total fats, gm.	50	137	65	(140)
Total fats, % of all Calories	19	40	20	(42)

* The data for Italy and the United States are from Food and Agriculture Organization estimates for 1949, revised 1952, and from United States Department of Agriculture, September, 1950.[8] The data from Naples pertain to the fire department rations, supplemented by individual interviews in 1952. The data for Minnesota are from United States Food Consumption Surveys, FE 781,[9] and pertain to Minneapolis-St. Paul in the winter, spring, and fall of 1948, the values in parentheses being cruder estimates than the others. Note that the values for Naples are for the firemen (adults), while all others are per caput of total population.

The *vigili annonari* inspect the sanitation and prices in food shops, act as traffic aides in rush hours, and act as a sort of auxiliary police. Their work is very light, but they spend most of the day on their feet.

DIETS

Clinical examination and interview revealed no signs of nutritional deficiencies or complaints of gross food inadequacies. Though the diets were uniformly simple and cheap, none of the men complained of actual hunger or basic food inadequacy. Moreover, as will be seen below, the majority of them were as fat as comparable Americans. Meat, fish, milk, cheese, and eggs were definitely luxuries for all the men, the great bulk of the diet being bread, *pasta* (macaroni, spaghetti, etc.), and local vegetables. Sugar and potatoes were eaten only in very small amounts, and butter was never used. Fruits and very small amounts of cheese were quite regularly consumed.

The average dietary pattern is indicated in Table 1. For the firemen an average daily total of about 3,000 Cal. was eaten at the fire department, and of this the total fats accounted for about 600 Cal., or 20%. On the days at home the diet of the firemen was similar but possibly a little less abundant and even lower in fats. For the *vigili* only the values obtained for the consumption of major staples seemed reasonably reliable, but it was clear that, as for the whole of Italy, cereals provided

about two-thirds of all calories. The best estimate was that total fats provided between 15 and 25% of the total calories for the various persons, the average being very similar to that of the firemen.

For the whole of Italy, national food balance data supplied by the Food and Agriculture Organization of the United Nations (headquarters in Rome) indicated that 19 to 20% of the total calorie supply is provided by total fats. The data from Naples, though grossly defective in some respects, are adequate to assure us that the men studied by us conformed to the national pattern and that, for the group as a whole, total fats covered close to 20% of the total calories.

Table 1 also shows that the average diet in Minneapolis-St. Paul is basically very similar to that of the United States as a whole in regard to total calories, proteins and fats. In certain respects, then, comparisons between Naples and the Twin Cities in Minnesota may have at least rough validity as representatives of the respective nations.

METHODS

The men reported at the Institute one or two hours after the typical southern Italian breakfast of a cup of coffee, usually with milk, and a plain bread roll at most; very frequently breakfast consists only of coffee. Prior to blood sampling the men had been on their feet for several hours; consequently they were not in the basal state, in spite of a brief rest at the Institute.

Total serum cholesterol was measured with the procedure used for the past five years in the Laboratory of Physiological Hygiene.[7] The serum is separated within two hours, and two 0.2 ml. aliquots are doubly extracted with fresh Bloor's alcohol-ether mixture, the precipitate being washed three times with more Bloor's mixture. The extract is evaporated to dryness on a water bath, and the residue is taken up in chloroform. Color was developed at exactly 25 C. with fresh, colorless Lieberman-Burchard reagent, and the maximum (by serial readings) color was read in the Evelyn photoelectric colorimeter, using a 660 mμ filter. Blanks and four fresh cholesterol standards in chloroform are read in each batch. The procedure is repeated on further aliquots if the duplicates differ by as much as 20 mg. of cholesterol per 100 ml. of serum.

In five parallel series, involving over 200 different serum samples, this method has been checked against the Sperry-Schoenheimer-digitonin method, the latter averaging 4 to 8% lower. In the most recent comparisons there were 70 pairs of serum aliquots and the digitonin method averaged 6.3% lower than the method used here. This systematic discrepancy is thought to reflect losses in the digitonin method.

The standard error of measurement from duplicate serum samples was calculated in Minneapolis and in Naples from 200 and from 95 consecutive pairs of measurements, respectively, using the formula $S.E._{est} = (\Sigma\Delta^2/2N)^{1/2}$. In Minneapolis the value was $S.E._{est.} = \pm 4.6$ mg.; in Naples the result was $S.E._{est.} = 3.6$ mg. per 100 ml.

The Evelyn machine, chemicals, etc., used in Naples were brought from Minneapolis, and the cholesterol standards were rechecked in Minneapolis on return. Further to assure strict comparability of results, quadruplicate aliquots of two serum samples in Naples were carried through Bloor extraction and drying and half of the samples, as dried residues, were sent to Minneapolis for comparison with the analyses finished in Naples. The mean values were 165 and 200 mg. per 100 ml. in Naples, 168 and 206 mg. in Minneapolis.

Electrocardiograms were recorded in the Naples Institute of Work Medicine with a Siemens (optical) apparatus. The recordings were extremely satisfactory in regard to stability of baseline and freedom from artifacts.

Body weight and height were measured in socks and underwear. For comparison purposes relative body weights were calculated as percentages of the average United States standards for corresponding height and age as given in the Medico-Actuarial Mortality Investigations of 1912, sometimes referred to as Davenport's standards. Subcutaneous fat thickness was estimated with calipers having a constant tension at all openings and are recorded here for the double

skinfold under a constant pressure of 10 gm. per square millimeter of (single) jaw face. Measurements were made over the triceps muscle midway between shoulder and elbow joints and on the belly midway between the umbilicus and the crest of the ilium.

COMPARISON OF FIREMAN AND *VIGILI*

In regard to serum cholesterol concentration, at least, the firemen and the *vigili* are not significantly different, as shown by Table 2. It should be noted that the age means and distributions are very similar in the two groups and that both groups are, on the average, well nourished as judged from body weights relative to United States standards.

The data in Table 2 lead to two important conclusions. First, it is apparent that for further statistical analysis it is justifiable to combine the two groups of men. When the cholesterol means are adjusted exactly, by regression analysis, to age

TABLE 2.—*Comparison of Clinically Healthy Firemen and Vigili Annonari in Naples, 1952*

	Men, No.	Age, Yr.		Relative Weight, % U. S.		Cholesterol, Mg./100 Ml.	
		Mean	S. D.	Mean	S. D.	Mean	S. D.
Firemen	50	34.5	9.4	103.6	12.7	218.6	35.9
Vigili	33	37.0	8.0	102.8	15.5	224.5	45.3
All men	83	35.5	8.9	103.3	13.8	220.9	39.7

TABLE 3.—*Relationship Between Age and Serum Total Cholesterol Concentration in Clinically Healthy Neapolitans*

Men, No.	Age, Yr.		Cholesterol, Mg./100 Ml.			
	Range	Mean	Mean	S. D.	a *	b *
40	20-34	27.93	209.8	38.7	123.1	3.10
50	27-40	34.18	224.6	38.4	175.1	1.45
39	30-40	35.13	228.3	40.8	199.1	0.83
58	30-48	38.40	228.7	38.5	212.7	0.37
43	35-54	42.58	231.3	38.2	236.5	—0.12
28	40-54	45.39	230.9	40.4	226.8	0.09

* The values for a and b are the constants in the regression equation, obtained by least squares: Cholesterol $= a + b$ (age).

35.0 for both groups, the mean cholesterol difference becomes only 4.4 mg., and a difference as large or larger than this would be predicted to occur by chance in over 20% of similar group comparisons. And, second, the data strongly suggest that the difference in habitual physical activity of the two groups has no important effect on the serum cholesterol level.

AGE-CHOLESTEROL RELATIONSHIP

Preliminary inspection of the data indicated that the relationship between serum cholesterol concentration and age over the full range covered here (20 to 54 years) must be curvilinear but that over more limited age ranges deviation from rectilinearity could not be established.[10] Accordingly, regression analysis was carried out with successive overlapping age ranges, and the results are summarized in Table 3.

From age 20 to the early thirties there is a marked age trend, the serum cholesterol concentration rising on the average about 3 mg. per 100 ml. per year. Both

the absolute concentrations in these ages and the age trend closely resemble the findings on a large number of clinically healthy men in Minnesota.[7] After 30 years of age, however, the age trend diminishes rapidly and there is no significant further rise. This is in marked contrast with the findings in Minnesota, where an average rise of the order of 2 or 3 mg. per 100 ml. continues into the fifties. Similar continuing age trends have been reported from elsewhere in the United States.† The net result is that for the age range 45 to 55 the United States "norms" are some 30 mg. per 100 ml. higher than the present values for Naples. Finally, it may be observed that in all age ranges, both in Minnesota and in Naples, the variation between individuals is substantially the same, the standard deviation being around 40 mg. per 100 ml.

OBESITY-CHOLESTEROL RELATIONSHIP

It will have been observed in Table 2 that, as judged by height-weight standards, the Neapolitans were, on the average, at least as obese as their American counterparts and that there was no significant difference between the firemen and the *vigili* in this respect. The same conclusions hold, at least approximately, when the skinfold thickness is the criterion, but exact comparison with American men is not possible because of slight differences in the calipers and technique.[13] The cholesterol differences between these Neapolitans and American men of the same ages obviously cannot be ascribed to differences in relative obesity.

TABLE 4.—*Partial Correlation Coefficients, Age Held Constant, Between Serum Cholesterol Concentration and Relative Obesity, the Latter Measured by Relative Body Weight and Separately, by Skinfolds*

	Relative Weight	Skinfold
Ages 21-32	0.322	0.243
Ages 31-54	0.169	0.145

Among the Neapolitans, the question of a relationship between relative obesity and serum cholesterol concentration, independent of age, was investigated by means of partial correlation analysis, using, as independent measures of relative obesity, both relative body weight and the thickness of the subcutaneous fat. For the latter the sum of the skinfold thickness over the triceps and on the abdomen was used. Because of the curvilinear regression between serum cholesterol and age (ignoring relative obesity), the data were treated for two separate age ranges, within neither of which departure from rectilinearity was statistically significant. The results are summarized in Table 4.

None of the partial correlation coefficients in Table 4 is statistically significant at the 5% level, the value of r (partial) $= 0.322$ for relative body weight versus cholesterol at ages 21 to 32 being significant only at the 6% level. However, since all the coefficients are of the same sign, they suggest that there may be a small, unimportant direct relationship between serum cholesterol and relative obesity, independent of age.

These findings are in agreement with several other sets of data. In 191 clinically healthy middle-aged Minnesotans there was a slight, statistically insignificant, difference (9.9 ± 7.7 mg. per 100 ml.) between the 64 thinnest and the 63 fattest men

† References 11 and 12.

in the series.[14] In poor Spaniards, many of whom were obviously generally undernourished, there was only a trivial relationship ($r = 0.24$) between relative obesity and serum cholesterol concentration, and in Spaniards of the professional class there was no relationship at all when the effect of age was eliminated.[15]

ELECTROCARDIOGRAPHIC DATA

Electrocardiographic studies on clinically healthy men in Minnesota have consistently shown highly significant differences in many items when young men are compared with men in the age range of 40 to 55 years.[16] In the data from Naples there were electrocardiograms on 55 men corresponding to the Minnesota age groupings. In Table 5 are summarized the findings on some of the items which most consistently show a marked age trend in Minnesota.

TABLE 5.—*Comparison of Electrocardiographic Age Trends in Younger and Older Clinically Healthy Neapolitan Men with Healthy Minnesotans of Similar Age*[16*]

				Axes	
	P-R	ΣQRS	ΣT	QRS	T
1. Naples, mean *Y*	13.89	24.42	4.70	43.07	34.59
2. S. D., line 1	1.82	6.24	1.49	30.56	21.68
3. S. E., line 1	0.36	1.22	0.29	5.99	4.25
4. Naples, mean *O*	13.50	19.90	3.90	41.18	39.61
5. S. D., line 4	1.29	5.96	1.32	23.10	23.19
6. S. E., line 4	0.24	1.13	0.25	4.37	4.38
7. Naples, line 1 — line 4	0.39	4.52	0.80	1.89	—5.02
8. S. E., line 7	0.428	1.647	0.381	7.326	6.052
9. Minn. *Y* — *O*, means	—0.67	7.54	1.85	28.98	9.91
10. S. E., line 9	0.206	0.789	0.247	2.838	2.309
11. Line 9 — line 7	1.06	3.02	1.05	27.09	14.93
12. S. E., line 11	0.47	1.83	0.45	7.86	6.48
13. t = line 11/line 12	2.23	1.65	2.31	3.45	2.31

* *Y*, age 21 to 32; *O*, age 40 to 54. P-R interval is given in 0.01 second, ΣQRS and ΣT in standardized mm. (= 0.1 mv.), axes in degrees. The standard errors of the differences are computed from the pooled variances. The values of t for specified levels of statistical significance (d.f. = 341) are 5% = 1.96; 2% = 2.33; 1% = 2.58; 0.1% = 3.29.

Table 5 shows that the Neapolitans, compared with the Minnesotans, show smaller age declines in QRS and T potentials, less age trend towards left axis shift, and no lengthening of the P-R interval. The differences in regard to the age trends of the two populations for which these men are samples are significant at about the 2% level for P-R, ΣT, and T axis and the difference is significant at the 0.1% level for the QRS axis. The difference in the age trends of ΣQRS is significant only at the 10% level, but separate analysis showed that the Neapolitans have significantly less age decline in R_2 and R_3 than do the Minnesotans. The Minnesota standards for young men, incidentally, seem to have general validity for young American men, as indicated by their close agreement with the findings on 1,000 young American aviators.[17]

COMMENT

After completion of the field work on which this paper is based, it was possible to make additional studies of 59 clinically healthy businessmen aged 50 to 60 (mean, 54.4 years) in Minneapolis and St. Paul. Careful measurements were made of the individual voluntary dietary intakes over a period of one, and in many cases two, weeks, by Miss Sadye Adelson and assistants from the Bureau of Home Economics

and Human Nutrition of the United States Department of Agriculture. The details of these habitual dietary intakes will be published separately, but it is interesting that in these men the mean intake was 2,510 Cal. daily and that 40.2% of the total calories was provided by fats. The mean serum total cholesterol concentration in these men, measured precisely as had been done in Naples, was 280.2 mg. per 100 ml. These data further document the dietary and serum cholesterol differences between Minnesota and Naples. They indicate, in fact, that the mean serum cholesterol concentration at around age 50 is something like 50 mg. per 100 ml. higher in the Twin Cities men than in the Neapolitans, instead of the 30 mg. difference suggested earlier in this paper.

It is now clear that, independent of other factors, the total fat content of the diet, or the proportion of the total metabolism supported by fats, exerts a powerful influence on the serum cholesterol level in man.‡ Over a wide range of variation, differences in dietary cholesterol intake exert little or no effect in man,§ but the fact that in some circumstances cholesterol and total fats tend to be parallel in the diet has caused considerable confusion.‖ It must be emphasized that in every controlled study in which the two factors have been really separated there has been no sign of an effect of dietary cholesterol per se; hence, whatever the cause of the peculiarity in serum cholesterol in the present Neapolitans, there is no reason to believe that the low cholesterol content of the diet is involved.

In addition to the question of the relationship between diet and serum cholesterol, a major reason for undertaking the present study was the problem of the relationship between diet and serum cholesterol on the one hand and the incidence and development of atherosclerosis, and attendant coronary and myocardial disease, on the other. This is not the place to present detailed data and analysis of vital statistics,¶ but it may be stated here that the evidence is overwhelming for concluding that the incidence of coronary and myocardial disease among middle-aged men in the United States is far greater than in Italy. This is significant in view of the cholesterol and electrocardiographic data from Naples, presented here. Evidence from Spain on diet, serum cholesterol, and heart disease indicates similar relationships.[15]

In a population sample study in the Netherlands, where the diet is moderately high in fats, it appears that there is an age-cholesterol trend somewhat like that in Minnesota, but one of the most interesting findings was a significant difference between Jews and Gentiles.[27] The higher value (difference of 13 mg. per 100 ml.) among the Jews was ascribed to their higher fat diet, and comment was also made about the apparently higher incidence of coronary disease among the Jews. Though the Dutch evidence is not definitive, it is in harmony with the picture that emerges from the present study in Naples as well as the findings in Spain.

It is of interest that the younger men in all of the groups studied—Minnesotans, poor and rich Spaniards, and Neapolitans—show only small variations from a single pattern in regard to serum cholesterol in spite of great dietary differences. The young men studied by Tanner [29] in England may be added to this list. By age 40, or even earlier, however, the dietary difference appears to be reflected in the serum.

‡ References 1-6.

§ References 18-23.

‖ References 24-27.

¶ References 3, 6, 15, and 28.

The sensitivity to the diet seems to change with age and to coincide with the age trend of atherosclerosis and coronary heart disease as indicated by vital statistics and postmortem studies such as reported by White and his co-workers.[30]

SUMMARY

Clinically healthy men 20 to 55 years old were studied in Naples, Italy, and were compared with findings from Minnesota, with regard to diet, serum cholesterol, obesity, and electrocardiographic items. Total fats provided about 20% of the total calories in the diet of the Italians, or about half that of the Minnesotans. Both population samples were equally fat and averaged slightly more than standard United States averages for given height and age.

From age 20 to the early thirties the average total cholesterol concentration in the serum of the Italians rose about 3 mg. per 100 ml. annually and corresponded closely with the Minnesotans in this regard and in the absolute concentration at given age. Thereafter, in sharp contrast with the Minnesotans, the Italians showed no further age trend, so that by age 50 there was a mean difference of about 30 mg. per 100 ml. between the population samples.

In the Italians, as in the Minnesotans, when the factor of age was eliminated statistically, there was no important relationship between serum cholesterol concentration and relative obesity as measured by either body weight or skinfold (subcutaneous fat) thickness.

Electrocardiographic comparisons showed statistically significant differences between the Italians and the Minnesotans in regard to age trends. The age trend to left axis deviation and prolongation of P-R and diminution of QRS and T potentials, so marked among the Minnesotans, was small or absent among the Italians.

The correspondence of these findings with recent data from Spain and England, and their relevance to the incidence of atherosclerosis and mortality from degenerative heart disease, is discussed.

Dr. Alfonso del Vecchio gave laboratory aid. The electrocardiograms were obtained through the Istituto di Medicina del Lavoro dell'Università.

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CHRONIC PANCREATITIS—PATHOGENESIS AND CLINICAL FEATURES

Study of Twenty-Eight Cases

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THE MECHANISMS concerned in the pathogenesis of chronic pancreatitis still remain a matter of some dispute despite interest in the disease for many years. Much of the discussion has centered around the relationship of accompanying biliary tract disease, and only recently has the confusion on this point become lessened. Moreover, earlier concepts to the contrary, chronic pancreatitis is not rare, nor is its symptomatology ill-defined. Part of the difficulty in obtaining a clear picture of this entity from reading of the past literature is due to artificial separation of cases into groups based on such criteria as the presence or absence of pancreatic calcification or the degree of functional abnormality evident. Insofar as such case differences are merely expressions of the variations in the disease manifestations, it would seem to detract from basic understanding to consider them separately.

During the three-year period January, 1950, to January, 1953, a total of 28 cases of chronic relapsing pancreatitis were observed at the Veterans Administration Hospital, Providence, R. I. These constituted 56 hospital admissions.

The information obtained by study of the patients and their records is thought to serve to emphasize, and perhaps clarify, certain points in regard to (1) the etiology, pathogenesis, and life history of the disease; (2) diagnostic features; (3) complications arising from the inflammatory reaction in the pancreas; (4) x-ray study; and (5) efforts at treatment. Pertinent information with regard to the cases will be presented in table form. A case with autopsy will be recorded in more detail.

ANALYSIS OF CASES

Etiological Factors.—Excess alcohol intake has been connected with the occurrence of both acute and chronic pancreatitis.* The relative importance of this factor varies considerably in the literature.† The group of cases herein reported serves to reemphasize the apparent causal relationship of alcohol to the development of chronic pancreatitis. Of the 28 patients, 19 (68%) were chronic alcoholics. In many the onset of the attacks of pancreatitis promptly followed intake of alcohol, and, indeed, the alcoholism often took the form of periodic bouts coinciding with the episodes of pancreatitis. As progress of the disease took place over a period of time, the amount of alcohol necessary to precipitate an attack frequently diminished, so that a history of only one or two drinks preceding the attack was not uncommon. The mechanism by which the intake of alcohol may be related to production of pancreatitis will be spoken of later.

From the Medical Service, Veterans Administration Hospital.

* References 1-6.

† References 1-7.

Of the 28 patients, 9 were not classified as chronic alcoholics, although 4 of these admitted to drinking in moderation. Five patients denied alcoholic intake. Of these, three were severe psychoneurotics with predominantly anxiety symptoms, one had undergone cholecystectomy and entered with a stone in the common bile duct, and one had previous perforated gastric ulcer with subsequent subtotal gastrectomy.

Only six patients had evidence of disease in the biliary system at some time in their course. Stones were present in the gall bladder in three, and in a fourth a stone was impacted in the distal portion of the common bile duct. The remaining two had been previously hospitalized for cholecystitis.

Sex and Age.—A higher incidence of the disease in males has been well documented.‡ All patients herein reported on were men, owing to the particular type of hospital population. The youngest patient was 27 and the oldest 74 years. The majority of cases (71.5%) occurred in the age group of 30 to 50 years. Although the character of the hospital population would exclude persons under 20 years of age, there would not be a similar exclusion of the older age groups.

Symptoms.—The symptoms of chronic pancreatitis are oftenest due to the inflammatory reaction in the pancreas but may be due to disturbances in related organs. The duration of symptoms prior to admission varied from 9 hours to 22 years. In four cases it could not be determined. Fifteen patients (58%) had noted symptoms for two to eight years.

Symptoms of the Acute Attack: Upper abdominal pain, nausea, vomiting, weight loss, and diarrhea were the cardinal symptoms. The severity of the symptoms in general varied with the severity of the attack, but usually intense pain and repeated vomiting were noted. Of the 56 admissions pain was noted in 52, and its duration, location, and radiation patterns are recorded in the following tabulation.

Location		Radiation		Duration	
Epigastric	40	Back	23	Hours	5
L upper quadrant	7	Shoulder, L.	6	1 to 4 days	23
R upper quadrant	5	Shoulder, R.	1	5 to 8 days	12
		L upper quadrant	10	8 + days	3
		R upper quadrant	10	Undetermined	9
		Generalized	1		
		None	16		

The diarrhea was not profuse and when present consisted of three to five loose stools a day, usually subsiding at the time the pain subsided. Hematemesis and melena had occurred in the past in four patients but was not seen in the admissions here. In one of these it had been associated with a peptic ulcer. All were severe alcoholics. The occurrence of hematemesis has been noted in cases of pancreatitis without other demonstrable cause. The presence of gastritis, secondary to either alcohol or pancreatitis, seems a logical explanation. A significant symptom seen in 26 of the 46 admissions in which it was recorded was weight loss. Not infrequently it exceeded 10 lb. (4.5 kg.), and in one case it exceeded 27 lb. (12.2 kg.). Unless pancreatic insufficiency or associated debilitating disease developed, the weight was regained during convalescence from the acute episode. The poor dietary habits of the alcoholic plus the gastrointestinal dysfunction due to the pancreatitis are thought to be the reasons for the weight loss. This feature plus the general lack of obesity is quite different from the nutritional status in primary cholecystic disease.

‡ References 1-8.

The frequency of occurrence of attacks varied from daily, in three patients, to less than one a year, in two. Most patients noted three to four attacks a year, although this was rather variable in a given case. Between episodes of pancreatitis most patients felt well and had few or no dyspeptic symptoms. Other writers have found dyspepsia frequent.§ The general absence of dyspepsia in the cases observed in this group was a helpful clue in drawing attention to the pancreas, rather than the upper gastrointestinal tract and gall bladder, as the site of primary pathology.

Examination.—Examination frequently revealed evidence of alcoholism and weight loss. There was moderate to marked epigastric tenderness, and occasionally spasm, and in patients with abscess or cyst a mass was palpated. Fever was either absent [22] or of low grade, being 99 to 100 F. in 13 admissions, 100 to 101 F. in 10 admissions, 101 to 102 F. in 6 admissions, and over 102 F. in 5 admissions. None exceeded 102.4 F.

Laboratory Data.—Table 1 demonstrates the variable incidence of the abnormalities, depending on the location and amount of pancreatic destruction, as well as the amount of disturbance in neighboring organs. Repeated attacks of inflammation in the pancreas may cause progressive destruction of acinar and/or islet tissue, with resulting loss of function, varying in degree in a given case. Tests of function may, therefore, range from showing no abnormality to demonstrating severe acinar and islet-cell insufficiency, with creatorrhea, steatorrhea, and diabetes. Follow-up of early cases might be expected to show progression of the evidence of functional abnormality with time in those in whom the inflammatory reaction is progressive. The end-result in some patients is severe destruction of the pancreas, so that secretion of pancreatic enzymes is at a low level. At this point an episode of pancreatitis may not be accompanied by increase in the level of circulating enzymes. The creatorrhea, steatorrhea, and glycosuria may be transient and mild during an acute attack.‖ The transient nature of the increased liberation of the pancreatic enzymes in the blood and urine is well known. Creatorrhea was present in nine cases (32%). In one it was transient, in six mild, and in two severe. Steatorrhea was transient in one, mild in two, and severe in two. Abnormal glucose metabolism, measured by either glycosuria or an abnormal glucose-tolerance curve, was present in eight cases, in one of which it was transient. Insulin was required by only one patient. The serum amylase was measured on 50 admissions and found to be elevated in 21. In two cases with low serum amylase, failure of elevation was noted after stimulation of the pancreas with bethanechol (Urecholine [9]), suggesting significant loss of acinar function.

Hepatitis may occur in association with cases of chronic pancreatitis ¶ and may manifest itself by abnormality in liver function, usually transitory in nature. The thymol turbidity was elevated in 11 of the 27 admissions in which it was measured. Sulfobromophthalein (BSP) excretion was determined in 10 admissions and was found to be impaired in 2. Serum protein level was normal in those instances in which it was studied, with the exception of that determined terminally in the patient

§ References 5-7.

‖ References 6, 7, and 14.

¶ References 6 and 14.

TABLE 1.—*Clinical and Laboratory Findings**

Patient	Date	Age, Yr.	Alcoholism	Gall Bladder Disease	Neither	Pain	Vomiting	Diarrhea	Wt. Loss	Temp.	Amylase	Steatorrhea	Creatorrhea	Bilirubin, Mg./100 Cc.	Thymol Units	B S P	W B C	Hb. Gm.	Glucose Met.	Comment
F. K.	4/51	37	+	0	..	+++	+	+	0	101	303	0	0	..	..	..	9,250	12	0	Dx not made during many prior attacks
W. S.	4/52	34	+	0	..	+++	+	..	0	100.4	162	..	..	..	..	..	26,000	13	0	Gastric res. bleeding duo. ulcer 1951
	8/52					+++	+	0	0	N	102	..	..	..	..	..	10,100	16	..	DT's, second attack pancreatitis
F. S.	4/51	42	+	0	..	+	+	0	+	99	62	+0	+0	0.2	5	..	6,250	15	+	Prior hematemesis, cause not demonstrated
	7/51					+++	+	0	+	99.2	81	+	+	..	..	..	10,250	12	0	Steatorrhea improved with pancreatin
	8/51					+++	+	+	0	N	...	+	+	..	..	..	8,050	11	+	DT's
	11/52					++	+	+	+	N	13	+	+	..	..	..	8,900	11	+	DT's, no rise serum amylase with Urecholine
	1/53					++	+	+	+	99.8	73	+	+	..	..	..	17,000	13	+	Continues to drink
F. D.	4/52	42	+	0	..	+++	+	0	0	N	165	..	..	..	..	..	9,100	16	0	5 yr. recurrent pain, previous Dx neurotic
R. B.	8/51	44	+	0	..	+++	+	+	+	101	450	0	0	0.4	21	..	26,550	15	0	Onset 1950, two prior attacks
	12/51					+	+	..	0	99	52	..	..	0.7	4	..	11,200	13	0	Alcoholic polyneuritis
	7/52					++	+	+	0	99	113	0	0	..	..	..	6,450	15	0	Attack subsiding on admission, DT's
	1/53					++	+	0	0	100.2	284	0	0	..	..	..	15,500	17	0	Typical attack, DT's developed
P. I.	12/50	31	0	0	Psycho	++	+	0	0	99	151	..	..	..	..	..	14,000	12	0	Onset 1948, attacks LUQ pain, calcification
G. R.	1/51	40	+	0	..	+++	+	0	..	100	328	..	..	2.3	3	..	17,900	13	0	Shock, DT's, beriberi, pancreatic calcification
F. R.	9/51	60	0	0	+	++	+	+	0	N	530	..	..	0.7	6	..	12,650	13	0	Gastric res. 1950 perf. gastric ulcer, 1st attack p.
	3/52					++	+	0	0	N	35	..	..	0.6	..	..	8,200	15	0	2d attack subsiding on admission
D. L.	2/52	33	0	+	..	+++	+	0	0	102	376	0	0	5.3	2	..	18,800	14	0	2 attacks in one month with icterus
	2/52					+++	+	0	0	101	407	0	0	8.1	2	..	.....	..	0	CBD stone removed, asymptomatic since
O. H.	6/52	42	+	0	..	++	+	..	..	99.6	157	0	0	1→0.2	6→2	N	12,600	13	+0	Onset 1946, hematemesis 1947, intoxicated
D. P.	8/51	27	0	0	Psycho	+++	+	+	+	99.8	125	..	0	..	..	..	19,353	13	0	Prior attack Dx gastroenteritis, calcif. in pan.
	4/52					+++	+	+	..	N	66	0	0	..	..	..	8,400	16	0	Attacks every 3-4 months
O. R.	5/52	57	+	0	..	History	0	+	+	N	...	+	+	0.6	4	..	6,900	13	+	No pain here, steatorrhea improved by pancreatin
A. W.	5/50	45	+	0	..	++	+	..	+	100	...	..	..	..	3	12%	12,000	15	..	Onset 1950 bouts epig. pain ff alcohol usually
	7/50					++	+	..	+	99.6	...	..	..	0.2	6	..	9,500	14	0	Attacks at weekly intervals
	5/52					+++	+	0	0	100	358	0	+	0.3	4	N	6,340	14	0	Dx made for 1st time, pancreatic calcification
W. R.	7/51	42	+	+	..	History	+	..	+	N	36	0	+	..	..	..	10,000	14	0	Prior hosp., Dx pancr., cholecystectomy for stones Evidence prior fat necrosis at operation
R. M.	3/51	32	+	0	..	+++	+	0	+	100	...	..	..	0.4	4	..	8,750	13	0	Subphrenic abscess due to pancreatitis
	12/51					+++	+	0	..	99.4	30	..	..	0.3	6	N	13,100	13	0	4 attacks in the interim, still drinks
	10/52					++	+	0	0	101	459	..	..	0.7	..	N	20,000	13	0	Mass (? cysts), gradually decreased in size

J. M.	7/51	42	0	0	Psycho	0	0	0	+	N	54	0	+	0.3	5	N	11,200	11	+	Needed insulin, no pain, pancreatic calcif. No rise serum amylase with Urecholine
B. O.	1/50	42	+	0	..	+++	+	+	+	99.8	12	0	0	0.3	4	..	12,200	15	+	Onset 1943, cholecystectomy 1944, peripancreatic hematoma 1946 ff. by subphrenic abscess
	2/51					+++	+	+	+	N	344	0	+	1.1→0.2	9	20%	16,000	11	+	
	4/51					+++	+	0	0	100.6	112	..	..	..	..	..	16,000	14	+	Lt. sympathectomy, pain now RUQ
	3/52					++	+	+	0	101	186	0	0	..	..	..	17,000	14	+	Rt. sympath., attack 1 mo. ff. discharge
	10/52					++	0	..	0	99	122	..	..	..	..	..	15,550	16	..	Recurring attacks but milder
T. I.	6/50	74	+	0	..	++	..	+	+	N	92	+	+	0.4	4	..	6,400	9	0	Pul. tbc., steatorrhea improved on pancreatin
J. H.	6/51	32	+	0	..	History	+	+	..	N	72	0	+	..	..	..	6,800	14	0	6 yr. recurring attacks, not in pain here
A. H.	9/49	58	+	+	..	++	0	..	+	N	90	..	..	1.5	..	..	10,000	14	0	Pain 22 yr., cholecystectomy (see summary), autopsy
	8/52					++	+	..	+	N	74	0	0	2.2→2.9	9→13	..	11,800	13	0	
W. C.	12/50	59	+	0	..	++	0	..	+	N	103	0	0	..	..	..	8,700	15	0	4 yr. bouts pain, pancreatic calcif., epilepsy
	6/51					++	0	0	0	N	63	..	..	..	..	..	7,600	13	0	Recurring pain
	9/51					++	0	0	..	N	94	+	0	..	..	..	11,500	14	0	Paranoid, carcinoma of lung
J. S.	6/51	32	0	+	..	++	+	0	+	102	383	..	..	0.4→13	4	..	21,700	14	0	Cyst drained, CBD narrowed; stones in GB, none in duct
J. D.	5/50	36	+	0	..	+++	+	0	+	100	68	0	0	..	..	N	10,500	15	+	5 yr. episodes pain, pancreatic calcification
	10/50					++	+	0	+	102	276	..	..	0.2	5	N	11,850	13	0	Expl., CBD and GB neg., pancreas fibrotic
	12/50					++	+	0	+	102.4	87	..	..	..	..	..	6,800	13	0	Alcoholic psychosis developed
	11/51					++	+	0	+	99	89	0	+	..	..	..	11,000	14	0	Recurring pain continues, DT's
P. H.	12/51	58	+	0	..	+++	..	+	..	N	64	0	0	0.4	8	N	17,000	15	0	Pain since 1947, now daily, bilat. sympath. done
	9/52					+++	..	..	+	N	40	..	..	0.8	10	..	10,100	14	+	Explor., small pan. cyst, GB and CBD negative
A. D.	3/51	33	0	+	Psycho	+++	+	0	+	100	262	0	0	0.6	4	..	11,000	14	0	Onset 1943 LUQ pain, pancreatitis on admission
	5/51					++	0	0	0	N	...	..	..	0.4	2	N	5,000	15	0	Cholecystectomy for stones, pain recurred postoperatively
W. B.	4/50	56	0	+	..	++	+	..	+	102	40	+	0	0.7	4	..	32,000	9	+	Pancreat. 1948, cholecystectomy for cholecystitis 1949, infected pan. cyst drained here
J. C.	10/51	38	+	0	..	+++	+	0	..	101	477	0	0	..	..	..	13,450	13	0	1st attack, DT's developed
	12/52					+++	+	0	..	100	499	..	..	0.1	..	..	18,650	13	0	Several attacks in interim, DT's again
D. K.	10/52	34	0	+—	Psycho	++	+	0	..	N	151	0	0	1.1→5.9→0.8	3	..	7,720	14	0	CBD narrowed due to enlarged pancreas

* + = present. 0 = absent. .. = not recorded. Pain graded + to ++++ in severity. Psycho = psychoneurotic. Amylase determined by modified Somogyi method, N = 40 to 110 mg. Bilirubin, N = up to 0.8 mg. per 100 cc. (method of Malloy and Evelyn). Thymol turbidity, N = less than 5 units. Steatorrhea and creatorrhea estimated by microscopic examination of stool (qualitative). BSP, 5 mg. per kilogram dose, N = less than 5% retention in 45 min. specimen. Glucose metabolism, + = abnormal (diabetic curve), 0 = not abnormal.

who died. As all but one of the patients showing evidence of abnormal liver function were alcoholics, it is difficult to assess the role played by the pancreatitis in the disturbance of the functional integrity of the liver.

Jaundice was observed seven times. In three cases the elevated bilirubin level was associated with abnormality in other tests of liver function and cannot be clearly ascribed to other cause. Of the remaining four cases, three showed common bile duct obstruction, due, respectively, to a pseudocyst, a calculus, and enlargement of the head of the pancreas. The other patient was a chronic alcoholic with beriberi, heart disease, and delirium tremens, whose liver function was not studied except for thymol turbidity, which was normal. It is recognized that jaundice may be a sequel to chronic pancreatitis,# due to interference with bile flow in the common bile duct from either enlargement of the head of the pancreas, with subsequent distortion and narrowing, or involvement of the wall of the duct by the inflammatory process. This type of mechanism was seen only once, however, in the production of jaundice in this series of cases.

Anemia was seen in six patients and was mild except in two, one with advanced pulmonary tuberculosis and the other with an infected pancreatic cyst, whose blood cell count also showed a leukemoid response in the granulocytic series. White cell elevation to 10,000 or more occurred in 36 admissions, in 16 of which it exceeded 15,000. The correlation between serum amylase and total white cell count was poor.

The x-ray findings (Table 2) showed calcification in the region of the pancreas in 11 (39%), pressure defects in the stomach or small intestine due to the presence of pancreatic cysts in 4, irregularity of the descending duodenum in 2, and a deformed duodenal cap in 2. The so-called deficiency pattern in the small intestine was occasionally present. A cholecystogram demonstrated stones in two, and the gall bladder did not fill in four cases. The nonfilling was temporary in one case, following an attack of pancreatitis, normal filling taking place two weeks later. In another, subsequent exploration revealed a normal gall bladder. That there may be temporary failure of gall bladder visualization with cholecystography in pancreatitis has been emphasized.* This may not be recognized, and cholecystitis then may be erroneously considered the underlying pathology. Administration of barium without obtaining a prior flat film may obscure the presence of pancreatic calculi, and at times oblique films are necessary, when the calculi overlie the spine.

Complications.—Complications of the inflammatory reaction in the pancreas in the form of a pancreatic pseudocyst developed in four cases. Surgical drainage was accomplished in two, with relief of symptoms. Of the two not drained, one cyst was 2 cm. in size, was located in the head of the pancreas, and was calcified. In the other the mass was observed slowly to decrease in size and no operative procedure was performed. A peripancreatic hematoma occurred in one patient during a prior admission to another hospital. Its development was probably related to digestion of the wall of the splenic vein by the liberated activated pancreatic enzymes. A small pancreatic abscess was found in the autopsied patient. Subphrenic abscesses occurred twice.

Diagnosis.—The diagnosis was established by the presence of recurring abdominal pain in attacks, together with elevation of the serum amylase or evidence of

References 10 and 11.

* References 6, 12, and 14.

pancreatic calcification, creatorrhea, or steatorrhea. Surgical exploration and autopsy provided confirmatory information when carried out. The frequency with which the diagnosis had been overlooked, often for several years, is worthy of comment. In 10 patients the diagnosis was arrived at after 2 to 25 years, and in 6 instances one year elapsed, despite repeated abdominal symptoms. Most cases were misdiagnosed as peptic ulcer, gastritis, or gall bladder disease. In those with previous gastrointestinal

TABLE 2.—*X-Ray Findings*

Patient	Stomach	Duodenum	Jejunum-Ileum	Gall Bladder	Pancreas Calcification
F. K.	N	N	N	N	0
W. S.	Gastro-enterostomy	N	N	..	0
F. S.	N	Irregular descending duodenum	Segmentation	N	0
F. D.	N	N	N	N	0
R. B.	N	N	N	N	0
P. I.	N	N	N	N	+
G. R.	N	N	N	N	+
F. R.	Gastro-enterostomy	N	N	N	0
D. L.	N	N	N	Nonfilling	0
O. H.	N	N	N	N	0
D. P.	N	N	N	N	+
O. R.	N	N	N	..	+
A. W.	Hiatus hernia	N	Deficiency pattern	N	+
W. R.	N	N	N	Stones	0
R. M.	Distortion of lesser curvature due to extrinsic mass	Cap deformed	N	11/2/52 poor filling 11/16/52 N	0
J. M.	N	N	N	..	+
B. O.	1950, 1951, 1952 N	1950, 1951 N 1952 narrowed, displaced by mass ?	1950 N 1951 segmentation 1952 N	.. Prior cholecystectomy	+
T. I.	N	N	Segmentation	N	+
J. H.	N	N	N	N	0
A. H.	..	..	..	..	0
W. C.	N	N	N	N	+
J. S.	Extrinsic pressure on greater curvature	N	Extrinsic pressure in loop jejunum	Nonfilling	0
J. D.	N	Spastic	N	N	+
P. H.	1951 N 1952 displaced by mass	1951 N 1952 deformed	1951 N 1952 irregular jejunum	1951 N 1952 nonfilling	+
A. D.	N	Cap deformed	Hypermotility	Stones	0
W. B.	Extrinsic pressure on greater curvature	N	N	..	0
J. C.	N	N	N	N	0
D. K.	N	Irregular	Segmentation	Nonfilling	0

and gall bladder x-rays the abdominal complaints were frequently placed on a psychoneurotic basis. The high incidence of personality disorder in these cases would tend to increase the likelihood of such error.

COMMENT

The cases observed emphasize the following facts: The disease occurs, in general, oftenest in the 30 to 50 age group, and in men who are not obese and who have personality disorders, usually with chronic alcoholism. They present a characteristic pattern of repeated attacks of upper abdominal pain, nausea, vomiting, diarrhea, and

weight loss. Between attacks they are free from symptoms. If the patient has had a previous medical work-up, he may also add the information that his upper gastrointestinal and gall bladder x-rays were negative. From such a history one should suspect the diagnosis. Clinical confirmation may be difficult except when elevated serum enzymes are observed during an attack, calcification in the pancreas is visible by x-ray, or evidence of creatorrhea or steatorrhea not due to other cause is present. Study of pancreatic enzymes by duodenal intubation is time-consuming and often of inconstant result, so that it is not widely done. It is emphasized that in the presence of a characteristic history one should hesitate to explain otherwise abnormal findings in other organs in the upper abdomen, as these may be related to the pancreatitis.

The differential diagnosis which oftenest presents itself is cholecystic disease, in which recurrence of symptoms is also characteristic. The pain pattern of gall bladder disease is usually different. It is of shorter duration; often colicky, with radiation to the right infrascapular area, and occurs oftenest in the obese and in females. To make the clinical picture more confusing, gall bladder disease is a frequent finding in cases of pancreatitis.

Implication of the biliary system as the initiating factor in the pathogenesis of pancreatitis originated with Opie in 1901.[13] It is based on the demonstration of a common channel of communication between the common bile duct and the pancreatic duct at the ampulla of Vater, together with experimental production of pancreatitis by injection of bile † and other substances [13] into the pancreatic duct. In addition, the high incidence of biliary tract disease in pancreatitis has been considered circumstantial evidence of its etiological importance. It has been clearly demonstrated that a common pathway frequently exists [17] and that reflux of pancreatic enzymes into the biliary system takes place.‡ The reverse (reflux of bile into the pancreas) has, however, been less clearly demonstrated, and its occurrence is usually associated with artificial increase in pressure either at autopsy [22] or during cholangiography.[23] Those who predicate bile reflux as the chief mechanism in the production of pancreatitis fail to consider the following evidence: 1. Studies of the anatomical relationship of the pancreatic and the common bile ducts at the ampulla indicate that stones larger than 5 mm. would obstruct the duct of Wirsung or the ampulla, thereby preventing bile reflux.[25] In addition, Mann and Giordano,[18] from a study of 200 autopsies, believe that a stone could produce a common channel in only 3.5%. In none of the 11 patients who had acute pancreatitis could a common channel be produced by obstruction at the ampulla. Good results following division of the sphincter of Oddi has been offered as evidence toward confirming the bile reflux theory.[24] This procedure would improve drainage of pancreatic enzymes as well, however, if obstruction were present at the sphincter. 2. There is a lack of biliary disease in a large per cent of the reported cases of chronic pancreatitis [6] (confirmed in this group). 3. Similarity of the clinical and pathological features has been noted in patients with chronic pancreatitis regardless of the presence or absence of cholecystic disease.[26] 4. Failure to prevent recurrences of the pancreatitis following removal of the gall bladder occurs [27] and was noted in the present series. 5. There is experimental evidence that pancreatitis can be produced by obstruction of the pancreatic duct alone.[28]

† References 15 and 16.

‡ References 19-21.

Production of pancreatitis is related to rupture of the acini and ducts within the pancreas, liberating pancreatic enzymes, which are activated by tissue juices.§ In order for this to occur, there must be increase in the intraluminal pressure, which can only be caused by obstruction to flow in the ducts in combination with stimulation of the pancreatic acinar glands to secrete. Reflux of bile into the pancreas would not seem to be a prerequisite or a necessary accompaniment.

Stimulation of the pancreas occurs in response to both hormonal and neural influences. The hormone secretin, produced in the duodenum in response to food, hydrochloric acid, and alcohol, is carried by the blood stream to the pancreas, stimulating secretion of a watery discharge high in HCO_3 and low in enzymes. The pancreas responds to vagal stimulation by a viscid secretion whose enzyme content is high.

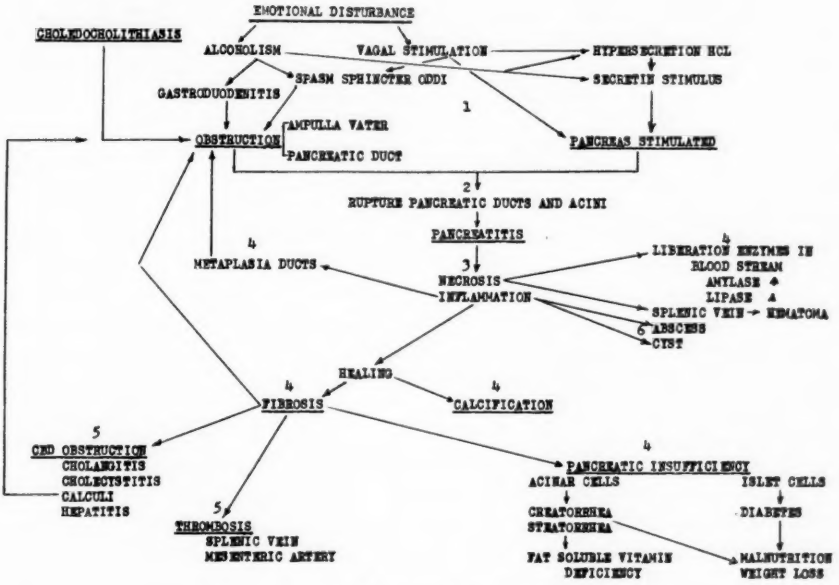

Fig. 1.—Pathogenesis and life history of pancreatitis.

Obstruction may occur at the sphincter of Oddi, owing to edema from duodenitis, or to spasm from HCl, alcohol, or vagal stimulation, or from impaction of a common duct stone. It is not surprising that the frequency of alcoholism in pancreatitis is apparent in both the literature and the group herein reported, in that alcohol influences both factors in the series of events leading to the onset of pancreatitis, namely, stimulation of the pancreas in the presence of obstruction of the outflow.

Taking into consideration the known physiology and pathology, and the etiological factors present in the reported series of cases, it was possible to arrange a diagrammatic outline relating the pathogenesis and life history of this disease. In doing so, it became evident that certain of the pathological changes that may occur in response to inflammation tend to perpetuate the disease by acting as further

§ References 29 and 30.

causes of obstruction to outflow of pancreatic secretions, thus setting up vicious cycles. The disease may become quiescent at a given stage, but in the presence of continuing exciting cause its relapsing nature becomes evident.

Initially depicted are the obstructive and stimulating factors acting on the pancreas and ducts (1), then rupture of the ducts and acini (2), with the result in terms of the types of inflammatory reaction (3), with their effect on the pancreas (4) and surrounding structures (5) and the complications thereof (6). Insofar as metaplasia of epithelial surfaces is most frequently seen in association with chronic inflammation, it would seem logical to attribute the frequent finding of metaplasia of the pancreatic ducts to the result rather than the initial cause of the pancreatitis. However, once developed, metaplasia would become a potentiating factor diminishing the diameter of the ducts. This, together with narrowing and angulation from fibrosis, may become a profound obstructing factor, so that one could visualize mild degrees of pancreatic stimulation resulting in significant increases in intraductal pressure (consistent with the progressive decreased tolerance to alcohol already commented on).

Although the information gathered here would not enable one to be dogmatic in furnishing an answer in regard to the relationship of the biliary system and pancreas in chronic pancreatitis, it does seem to confirm the assumption that in some cases a common duct stone may be instrumental in the production of pancreatitis by obstruction of pancreatic outflow at the ampulla. More often the pancreatitis is responsible for the disturbed biliary dynamics by mechanisms already alluded to, leading to stasis, inflammation, and thereby possible stone formation. The common denominator in all cases appears to be obstruction to pancreatic flow at the ampulla in the presence of active secretion, whether the obstruction be due to stone, edema, or spasm.

Treatment.—Treatment can be divided into medical and surgical measures. The medical measures are concerned with the management of the acute attack, an attempt to replace any deficient pancreatic secretions, and an effort to eliminate any known cause for other attacks. The acute attack is, perhaps, best treated with meperidine (Demerol) for relief of pain, atropine or methantheline (Banthine) to decrease gastric and pancreatic secretions and to inhibit action of the sphincter of Oddi, Levin tube gastric suction to prevent hydrochloric acid from reaching the duodenal mucosa for secretin stimulation, and probably antibiotics to diminish any local infectious process.

Surgical measures are indicated for treatment of many of the complications of the inflammatory process, such as the development of abscess, pseudocyst, and peripancreatic hematoma and for the removal of a diseased gall bladder or biliary calculi. However, the most frequent problem that requires solution in the cases of chronic pancreatitis is relief of recurrent attacks of pain. Several procedures based on different physiologic approaches to the problem have been devised for this purpose, including thoracolumbar sympathectomy,|| vagotomy,[33] vagotomy combined with subtotal gastrectomy,[34] sympathectomy plus vagotomy,[35] sphincterotomy,[24] and even pancreatectomy.[36] The details will not be reviewed here; suffice it to say that most authors report significant benefit in most of their cases. The indications for carrying out some procedure for the relief of pain are dependent on the severity of

|| References 31 and 32.

the disability encountered. Experience here is limited to two cases in which sympathectomy was performed. Although there was slight improvement in the intensity of the pain in one case, the results are not considered particularly beneficial. Both the patients were alcoholics, a fact which may have bearing on the selection of future cases.

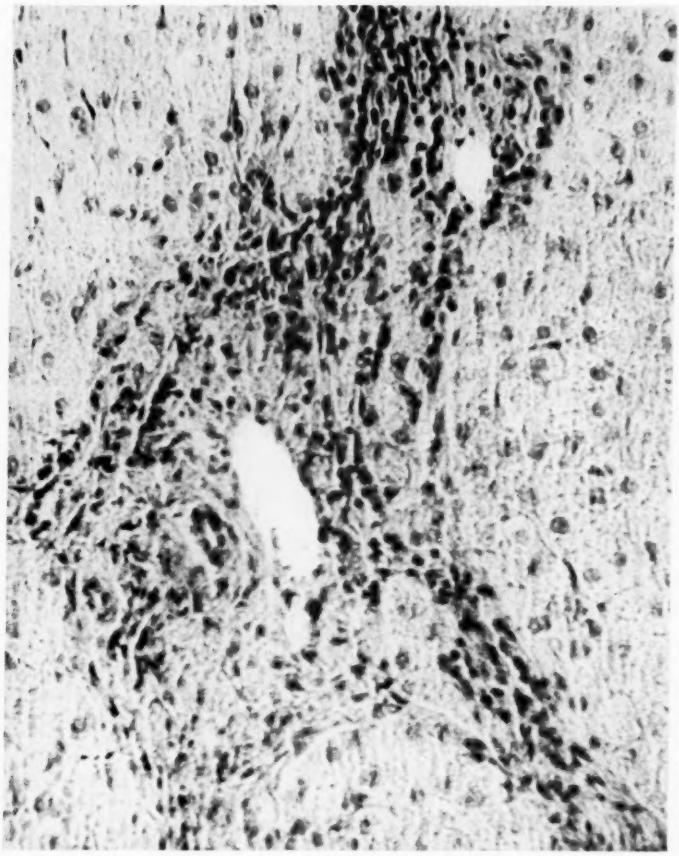

Fig. 2.—Liver biopsy specimen taken in 1949, showing increase in fibrous tissue in the portal areas together with cellular infiltration; × 280.

The following case study with autopsy findings is thought to illustrate many features of the disease process.

REPORT OF A CASE

CASE 20.—A. H., a 61-year-old white man, a mill worker, entered this hospital in September, 1949, giving a history of 22 years' duration of recurring bouts of epigastric pain and vomiting, each lasting about a week. In 1949 an episode of jaundice with with dark urine had occurred. He had gradually lost 27 lb. (12.2 kg.). For many years he had consumed large amounts of whisky, as well as other types of beverages.

Physical examination revealed evidence of weight loss and epigastric tenderness. His blood cell count, urine, fasting blood sugar, and serum amylase were normal. Bilirubin fluctuated between 0.9 and 1.5 mg. per 100 cc. preoperatively. Exploration disclosed an enlarged finely granular liver, an enlarged firm nodular pancreas, and a normal-appearing gall bladder. The common bile duct appeared normal, but instruments could not be passed into the duodenum. The gall bladder was removed and showed fibrous thickening of the serosa and mucosa, with some inflammatory cell infiltration consistent with chronic cholecystitis. The liver biopsy (Fig. 2)

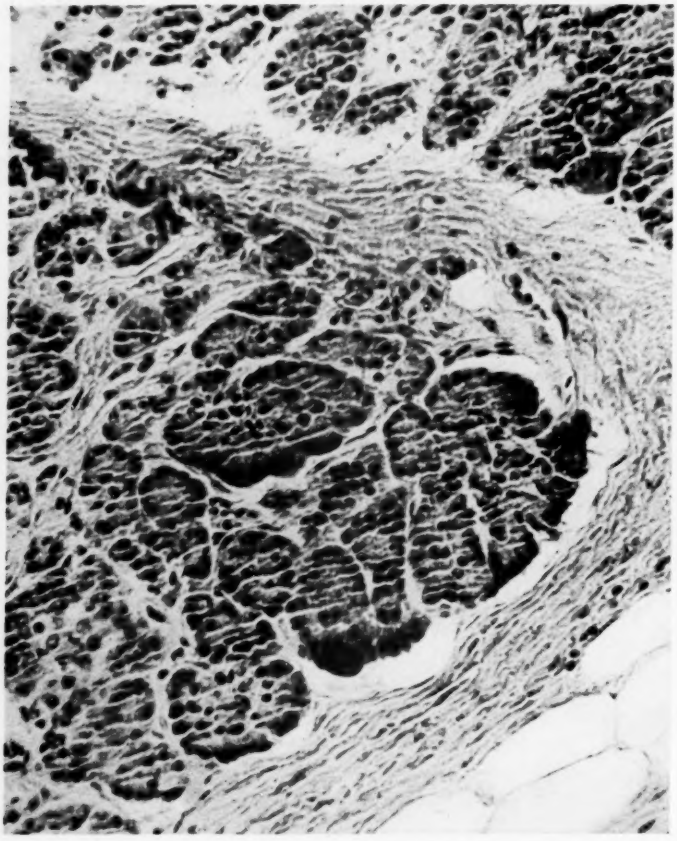

Fig. 3.—Pancreas biopsy specimen taken in 1949, showing interlobular fibrosis; × 280.

showed thickening of the capsule; increase in fibrous connective tissue, tending to enclose the liver in lobules, and cellular infiltration of the portal spaces. The changes were thought to represent chronic hepatitis. The pancreatic biopsy (Fig. 3) showed marked fibrosis and atrophy of the parenchyma. Dilated pancreatic ducts were noted. After operation the patient continued to have episodes of epigastric pain and vomiting at scattered intervals.

He was readmitted in December, 1952, because of continued upper abdominal pain and vomiting and the development of ascites. An accurate history was difficult to obtain, owing to cerebral arteriosclerosis and deterioration from alcoholism. He had also noted edema of the legs, exertional dyspnea, and chronic cough. Examination showed a chronically ill-appearing, thin, white man with slight icterus of the skin and sclerae. Temperature was 97 F., pulse rate 80, respira-

tion rate 26, and blood pressure 118/88. There were numerous spider angiomata and telangiectases on the cheeks. The abdomen was distended, with a fluid wave and shifting dullness. The liver was enlarged. The superficial veins in the abdominal wall were dilated. There was 2+ peripheral edema. The urine on admission contained a trace of albumin and was positive for bile. The blood cell count was normal. Serum bilirubin was 2.2 mg. per 100 cc., thymol turbidity 9 units, cephalin flocculation 4+, and total protein 5.2 gm. per 100 cc., with albumin of 2.6 gm. and globulin of 2.6 gm. per 100 cc. Serum amylase was 74 mg. per 100 cc. A chest x-ray revealed a tortuous aorta and an elevated right leaf of the diaphragm. A flat plate of the abdomen showed no abnormalities. The electrocardiogram was consistent with intermittent left bundle branch block. The hospital course was progressively downhill. Abdominal paracentesis revealed straw-colored fluid, with specific gravity of 1.005. No increase in fat or any undigested muscle fibers were found in stool examinations. The patient complained of epigastric pain intermittently, chiefly after meals. He had a progressive downhill course and died.

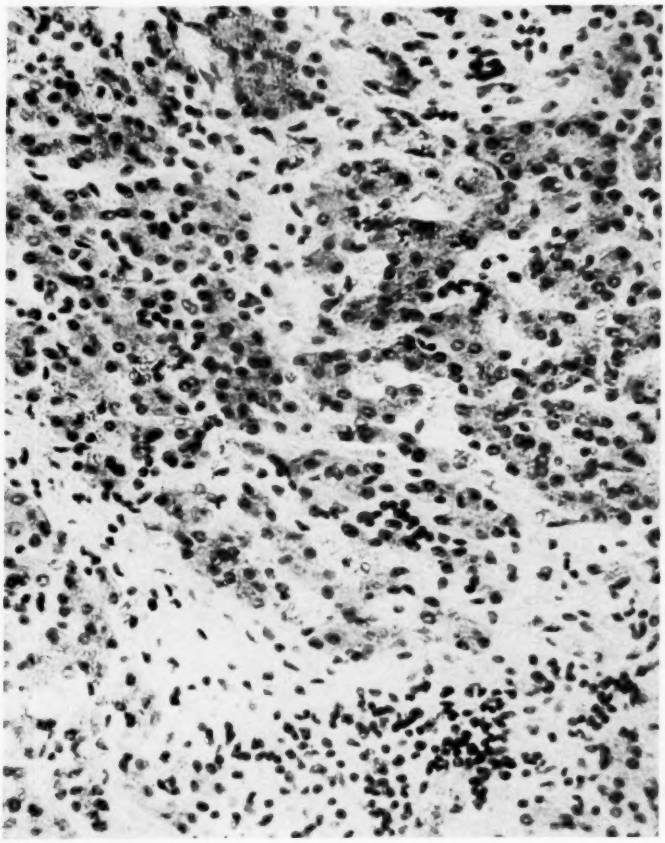

Fig. 4.—Liver autopsy specimen taken in 1952, showing portal fibrosis breaking the liver lobules into islands of varying size, with cellular infiltration of the portal areas; × 280.

Autopsy (Dr. Melbourne Burnett).—Gross Findings: The body was emaciated. Hemorrhagic areas were noted in the skin, and general atrophy of tissue was present. There was 3,000 cc. of

clear yellow fluid in the abdominal cavity and 200 cc. in each thorax. The bronchi contained purulent exudate, and the mucosa was hemorrhagic. The aorta was sclerotic, with a saccular aneurysm of the thoracic aorta. The liver weighed 750 gm. and the spleen 50 gm. The surface of the liver was smooth to granular, and the architecture was obscured. The gall bladder was absent. Proximal to the pancreas the common bile duct was dilated, measuring 2 cm. in circumference. The head of the pancreas was normal in size. The duct of Wirsung contained an

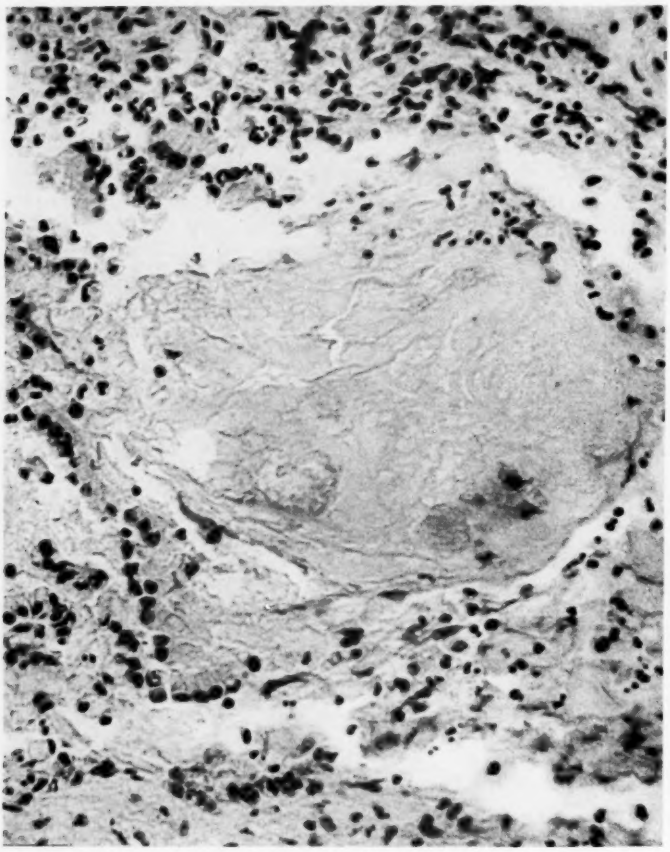

Fig. 5.—Pancreas autopsy specimen taken in 1952, showing dilated pancreatic duct with inspissated protein and exudate; × 280.

impacted 7 mm. calculus at the junction of the main and the secondary duct. Proximal to this the smaller ducts contained numerous smaller calculi. There was marked fibrosis of the pancreas, especially in the region of the head. There were some intact areas of pancreatic tissue near the tail. A few small abscesses were seen throughout the parenchyma of the body and tail. The adrenal glands were small. The mucosa of the stomach was smoothed out, and multiple hemorrhagic areas were present in it. The wall of the jejunum was thickened and edematous. The mucosa of the large intestine contained numerous circular raised granular areas. The left iliac vein contained an antemortem thrombus.

Microscopic Findings: The heart showed brown atrophy, the lungs hemorrhages and bronchopneumonia, the bronchi hemorrhages and ulcerations of the mucosa, and the spleen fibrosis of the red pulp and hemosiderosis. The capsule of the adrenal glands was thickened, and there was superficial fibrosis of the zona glomerulosa. There was atrophy of striated muscle. The lobular architecture of the liver (Fig. 4) was broken up into islands of varying size by fibrous

Fig. 6.—Pancreas autopsy specimen taken in 1952, showing diffuse interstitial pancreatitis; × 280.

strands arising from the portal areas and extending occasionally to the central veins. The liver cells contained heavy deposits of hemosiderin. The portal areas and fibrous strands were variably infiltrated with lymphocytes.

The pancreas (Figs. 5 and 6) showed marked distention of large and small ducts. Their lumens contained exudate of polymorphonuclear leucocytes and precipitated protein. There was intralobular and perilobular fibrosis of the parenchyma. The fibrosis varied from early granulation tissue to mature fibrous connective tissue. There were numerous focal areas of fat necrosis,

with abscess formation in the peripancreatic fatty tissue and in relation to the splenic vein. The islets were intact. There were numerous areas of necrosis in the mucosa of the colon. Final anatomic diagnosis:

1. Chronic pancreatitis
   (*a*) Pancreatic lithiasis
   (*b*) Chronic suppurative pancreatitis
2. Chronic hepatitis S49-122 of unknown etiology
   (*a*) Portal cirrhosis of liver
3. Acute colitis of unknown etiology
4. Generalized arteriosclerosis
5. Thrombosis of the left iliac vein

Comment.—The clinical findings, together with the information obtained at the laparotomy, in 1949, and the autopsy, in 1952, furnish the basis for reconstruction of the life history of the disease in this patient. Chronic alcoholism initiated recurrent attacks of pancreatitis. Healing of the acute inflammatory processes resulted in extensive fibrosis of the pancreas. The fibrosis impaired drainage in both the pancreatic and the common bile duct. The low-grade cholecystitis noted in 1949 could have been related to either the disturbed biliary dynamics or the pancreatitis itself. Stasis in the pancreatic duct favored recurrent acute inflammation, stone formation, and the development of diffuse, acute, and chronic inflammation within the gland.

The progression of changes seen in the liver were most interesting and difficult to evaluate in terms of etiology. In 1949 the pathological picture of cellular infiltration and increase in fibrous connective tissue (Fig. 2) suggested a form of chronic hepatitis. At death, three years later, there had been significant increase in the fibrous tissue (Fig. 4). Although the patient was a chronic alcoholic, the pathology is not characteristic of Laennec's cirrhosis. If it is assumed that the hepatic changes were related to the pancreatitis, the mechanism of production is not clearly understood.

SUMMARY AND CONCLUSIONS

Chronic relapsing pancreatitis is a relatively common disease. Fifty-six admissions were seen in a three-year period.

A high incidence of personality disorders and alcoholism is noted. Both factors are believed to be of etiological significance.

Symptoms of the disease are usually quite characteristic and consist of recurrent episodes of upper abdominal pain, vomiting, diarrhea, and weight loss. Between attacks the patients are usually symptom-free. Despite characteristic symptomatology, many cases had not been correctly diagnosed.

Evidence of pancreatic insufficiency was present in approximately 30% of the cases.

In most instances associated biliary disease is believed to be a consequence of the pancreatitis. The reverse is true occasionally.

The results of sympathectomy were discouraging in the two cases in which it was performed.

A presentation of some of the etiological factors in relation to the pathogenesis and life history of the disease is made.

Mr. Edwin B. McDermott helped in preparing the illustrations.

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MEDULLARY CYSTS OF KIDNEYS

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PROGRESSIVE renal failure, when present in such varying diseases as chronic glomerulonephritis, chronic pyelonephritis, hydronephrosis, arteriolonephrosclerosis, and polycystic kidneys, is usually characterized by common clinical manifestations. Hypertension, retinopathy, edema, anemia, nitrogen retention, albuminuria, and cylindruria are usually present at some time during the course of the disease. Exceptions occur, of course, but in general the late manifestations are quite constant, regardless of the underlying renal process.

This paper deals with four cases which deviated consistently from this typical clinical pattern. In all these cases the kidneys were found to be small and contracted and to contain numerous medullary cysts. The clinical picture was characterized by insidious uremia and anemia alone, unaccompanied by the other stigmata of progressive renal failure. Three of these were taken from the files of the Presbyterian Hospital and one from the files of Dr. Warfield T. Longcope. In addition, reference is made to two cases from the literature.

REPORT OF CASES

CASE 1.—*A middle-aged woman developed nausea and vomiting three weeks before admission. This persisted despite an uneventful herniorrhaphy, and the patient died in uremia 10 days after operation.*

S. M., a 49-year-old white woman, was admitted to the Presbyterian Hospital on April 12, 1950, with a diagnosis of uremia. She had been well except for mild diabetes, controlled with diet alone, discovered two years before. At age 26, the time of her first pregnancy, she was told she had "kidney disease," but a second pregnancy was uneventful. About three weeks before admission she noted the gradual onset of persistent pain in the left inguinal region, and nausea and vomiting developed. Ten days later she was admitted to another hospital, where physical examination revealed a normal temperature, blood pressure 118/78, and a left femoral hernia, not incarcerated. Laboratory examinations disclosed a hemoglobin of 11.5 gm., 3,750,000 red blood cells per cubic millimeter, and 8,550 white blood cells per cubic millimeter, with a normal differential count. Urinalysis revealed a specific gravity of 1.006, albumin 10 mg. per 100 ml., no sugar, and an occasional white blood cell per high-power field. An uneventful herniorrhaphy was performed and no obstruction found. Postoperatively the patient developed increased nausea and vomiting and marked lethargy. The blood urea nitrogen was 75 mg. per 100 ml. three days postoperatively, and the serum creatinine 5.3 mg. per 100 ml. One week postoperatively the blood urea nitrogen had risen to 168 mg., the creatinine was 14.8 mg., and the blood sugar was 200 mg. per 100 ml. The urinary output during this period was

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described as "good," with single voidings up to 400 ml. The specific gravity of several urine specimens ranged between 1.006 and 1.012. The blood pressure ranged between 120/70 and 170/90. The patient had no transfusions and was given no sulfonamides. She was transferred to the Presbyterian Hospital one week postoperatively in critical condition.

Physical examination revealed a temperature of 95.8 F., pulse rate 80, respiration rate 28, and blood pressure 170/90. The patient appeared acutely ill, with Kussmaul breathing and a marked uremic odor to the breath. No papilledema, hemorrhages, or exudates were noted in the fundi. Dried dark blood was seen in both nares and on the palate. The lungs were clear, the heart was not enlarged, and there was a harsh apical systolic murmur transmitted to the axilla. A healing left inguinal incision was present, and the pelvic and rectal examinations revealed no abnormalities. No peripheral edema was noted.

Fig. 1 (S. M.).—Small kidneys showing multiple cysts, largely in the medulla, and obliteration of normal parenchymal architecture.

Laboratory studies revealed a hematocrit level of 25%, hemoglobin of 8 gm., 2,840,000 red blood cells per cubic millimeter, and 18,200 white blood cells per cubic millimeter, 90% polymorphonuclear leucocytes. The sedimentation rate was 85 mm. (uncorrected Westergren). Catheterization yielded 300 ml. of urine with a specific gravity of 1.010, 2+ albumin, 1+ glucose, 20 white blood cells per high-power field, no casts, and no red blood cells. Escherichia coli was cultured from the urine. The serum CO_2 was 19 mEq. per liter, serum chloride 89 mEq. per liter, serum sodium 124 mEq. per liter, blood urea nitrogen 254 mg., serum phosphorus 15.6 mg., serum calcium 6.7 mg., and blood sugar 104 mg. per 100 ml. Nose and throat cultures contained no hemolytic streptococci. A roentgenogram of the abdomen showed no renal calculi.

During the 24 hours following admission, the blood pressure remained in the neighborhood of 150/70 and the patient produced 700 ml. of urine. She developed coarse pulmonary rhonchi and was digitalized intravenously but continued to fail and died 24 hours after admission.

Autopsy.—The examination was limited to the abdominal cavity. The body was that of a moderately obese middle-aged white woman. The organs except for the kidneys were essentially normal.

The right kidney weighed 80 gm., the left 75 gm. (Fig. 1). The surface was made markedly irregular by the presence of numerous clear cysts measuring up to 1.5 cm. in diameter. The capsule was stripped with mild to moderate difficulty. The subjacent cortex was granular. On cut section, the parenchyma was honeycombed with numerous clear cysts varying in diameter from 0.5 to 20 mm. These were concentrated in the medulla, especially in the region of the pyramids. The pelves, calices, and ureters were not dilated and were lined by smooth epithelium and contained only a few small areas of hyperemia.

On microscopic examination the most striking feature was the marked cystic appearance, both in some areas of the cortex and throughout the pyramids. The cysts were lined with low cuboidal to squamous epithelium and contained a varying amount of amorphous eosinophilic

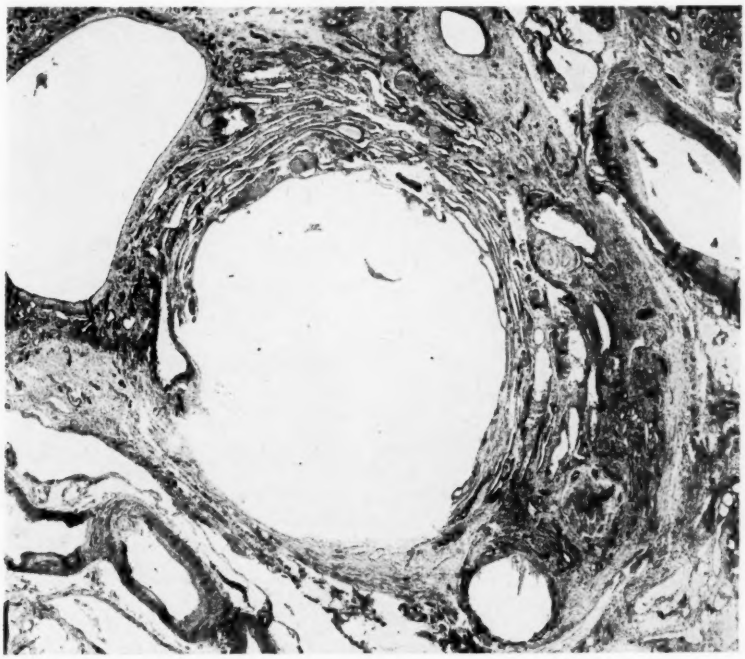

Fig. 2 (S. M.).—Photomicrograph of medullary cyst illustrating distortion and compression of adjacent tubules; × 16.

granular material. The glomeruli were reduced in number, and of these approximately 60% showed only hypertrophy and mild congestion. The remainder were fibrotic and hyalinized. There was no pericapsular fibrosis. Rarely, in hyalinized glomeruli, capsular-tuft adhesions were noted. No epithelial crescents were seen. Approximately 80% of the tubules were abnormal. Many were atrophic; others were slightly to markedly dilated, lined by thin epithelium, and contained only small amounts of granular eosinophilic material. In some of the small irregular atrophic areas there was a moderate lymphocytic infiltration. In one section, surrounding a cyst in the medulla, there was marked tubular distortion, with the tubules apparently coursing out around the cyst (Fig. 2). One cyst was seen to communicate with a tubule of normal caliber which was lined with cuboidal epithelium (Fig. 3). The small arteries and arterioles showed only mild proliferative changes. The mucosa of the pelvis was intact, and there was no subjacent inflammatory reaction.

The anatomical diagnosis was polycystic kidneys (medullary type).

CASE 2.—*A young man complained of weakness and vomiting six months before hospitalization. These symptoms became more severe, and dyspnea, muscle cramps, muscular twitching, coma, and death ensued.*

J. G., a 28-year-old white salesman, was admitted to the Presbyterian Hospital Feb. 13, 1941, with complaints of weakness and vomiting of six months' duration. He was in excellent health except for clubfoot, treated surgically in infancy, until the onset of the symptoms which brought him to the hospital. There was no history of hypertension, and the patient passed a physical examination for a life insurance policy three years before admission.

Seven months before admission the patient developed a mild nonproductive cough, which increased in severity and frequency until hospitalization. One month after the appearance of the cough he noted vomiting with more severe paroxysms of coughing, and for the four months

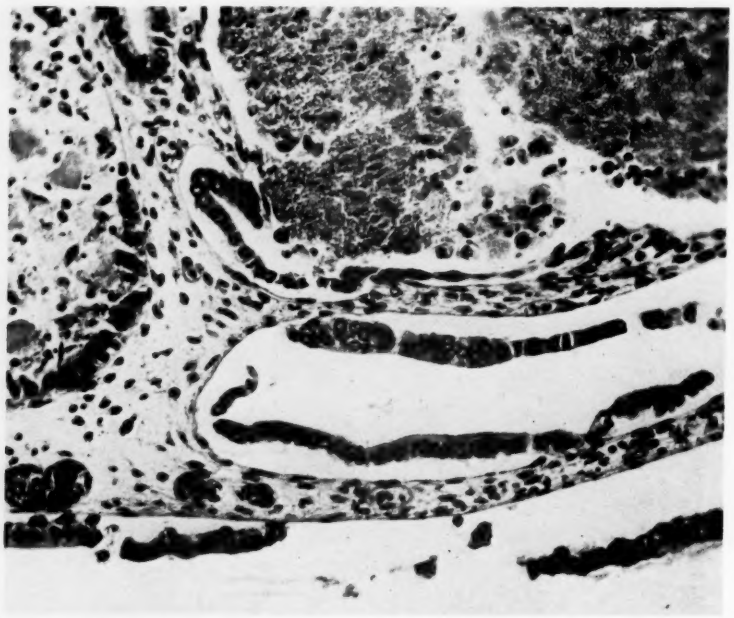

Fig. 3 (S. M.).—Photomicrograph showing a cyst (upper right), near the apex of a pyramid, with squamous epithelium continuous with normal tubular epithelium. Inferiorly is the partially desquamated transitional epithelium of the renal pelvis; × 430.

before admission he had noticed increasing fatigue, exertional dyspnea, and frequent muscle cramps. For the two weeks prior to admission there was marked exacerbation of all symptoms.

Physical examination revealed normal temperature, pulse, and respirations and a blood pressure of 140/80. The patient was a pale, chronically ill white man. The skin was sallow, dry, and thickened, with a diffuse excoriated, punctate, erythematous rash. The conjunctivae were pale, and the fundi were normal, with no papilledema, hemorrhages, or exudates. The breath was described as "aminous." The lungs were clear. The heart was not enlarged, and there was a soft apical systolic murmur. The liver was moderately tender 2 cm. below the right costal margin. A left clubfoot was noted, and the reflexes were hyperactive throughout. There was no peripheral edema.

Laboratory studies revealed a hemoglobin of 8 gm. and 2,590,000 red blood cells and 12,900 white blood cells per cubic millimeter, with a normal differential count. The sedimentation rate was 120 mm. (uncorrected Westergren). The urine contained 3 + albumin, 0 to 2 red blood cells per high-power field, and no casts. The serum albumin was 4.8 gm. per 100 ml.,

and the globulin was 1.8 gm. per 100 ml. The nonprotein nitrogen was 285 mg. per 100 ml., serum cholesterol 237 mg. per 100 ml., alkaline phosphatase 3.7 Bodansky units, serum phosphorus 7.1 mg. per 100 ml., calcium 10.9 mg. per 100 ml., CO_2 18 mEq. per liter, and chloride 87.7 mEq. per liter. The antistreptolysin titer was 71 units. A phenolsulfonphthalein test revealed no excretion of the dye in two hours. Roentgenograms of chest and abdomen were normal; cystoscopy revealed a normal bladder, and retrograde pyelograms showed "fuzzy" right middle and lower calices and a similar appearance in the left lower calyx.

During two and one-half weeks in the hospital the patient's course was progressively downhill. The serum nonprotein nitrogen rose, and muscular twitching and semistupor ensued. He died without the development of a pericardial friction rub or evidence of cardiac failure.

Autopsy.—The body was that of a thin young white man. There was a hard irregular 2.5 cm. mass in the right buttock. The left foot presented pes cavus and equinovarus.

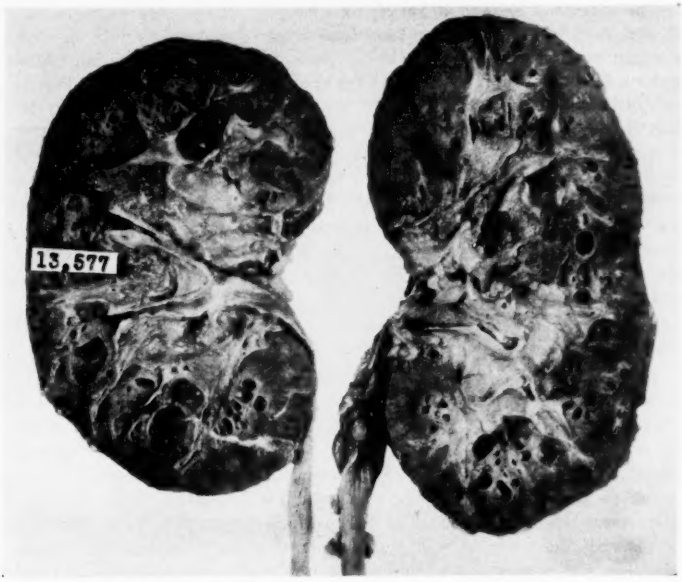

Fig. 4 (J. G.).—Small kidneys showing multiple medullary cysts with surrounding atrophic cortex.

The heart was not enlarged. There were gritty grayish deposits in a small area near the apex. Yellowish intimal plaques were scattered throughout both coronary arteries. The pancreas was grossly normal. The parathyroids weighed approximately 160 mg. each. The vertebral marrow was pale and there was decreased prominence of trabeculation. The mass in the right buttock was calcific.

The right kidney weighed 80 gm. and measured 9 by 5 by 4 cm. The left kidney weighed 70 gm. and measured 8.5 by 5 by 3 cm. (Fig. 4). The capsule stripped with ease, exposing a surface which presented small numbers of cysts, which were thin-walled and contained a water-clear fluid. They measured from less than 1 mm. to 8 mm. in diameter. The parenchyma was firmer than normal and cut with increased resistance. The cortex was narrower than normal and the number of glomeruli appeared reduced. A few small cysts were scattered throughout the cortex. The pyramids, although not blunted, were slightly smaller than usual and were in great part composed of smooth-walled cysts varying in size from less than 1 mm. to 8 mm. in diameter. The pelves and calices were not dilated or thickened. The ureters were patent throughout and were neither dilated nor thickened. Both renal arteries measured 2 to 3 mm. in diameter throughout their entire course. The walls were not thickened.

On histologic examination the area near the apex of the heart was seen to be the site of rather vascular scarring with extensive calcium salt deposition. Occasional areas of peripheral calcification were seen in myocardial fibers. There was extensive calcification in the media of the coronary arteries. The media of the aorta showed slight mucinous changes, and in places there was granular deposition of calcium. Elastic stain revealed no interruption of elastic fibers. Scattered through the pancreas were a number of small irregular cysts or dilated ducts, occasionally multilocular. They measured up to 1 mm. in diameter and were lined by flattened epithelium and contained irregular hyaline bodies, often in the form of convoluted ribbon-like structures. There was slight fibrosis about most of these cysts. In the enlarged parathyroids, chief cells predominated. In the marrow there were numerous areas of fibrosis.

The renal parenchyma was the site of extensive diffuse atrophy, with some small irregular areas of lymphocytic infiltration. Numerous small cysts were present, chiefly in the pyramids. They were lined by flattened epithelium and contained only a few fragments of eosinophilic material. The glomeruli showed a variety of changes. Many were partially or completely hyalinized, and most of the remainder were hypertrophied and only rarely showed thickening of the basement membranes. A small number showed extensive calcification. Although there was no crescent formation, mild pericapsular thickening was frequently seen. Capsular adhesions were rare. In some areas the tubules were markedly atrophic; elsewhere they tended to be quite enlarged, the lining cells hypertrophied. Hyaline casts were fairly numerous. A few collecting tubules contained polymorphonuclear leucocytes. Several arterioles and small arteries showed slight hyalinization of the walls. The renal arteries were less than half the usual caliber and there was a small calcific plaque in the peripheral zone of the media of one.

The anatomical diagnoses were polycystic kidneys (medullary type), congenital stenosis of the renal arteries, congenital cysts of the pancreas, congenital malformation of the foot, hyperplasia of the parathyroids, osteitis fibrosa, and calcifications in the heart, kidneys, thyroid, and subcutaneous tissues.

CASE 3.—*A young man noted muscle cramps, weakness, and finally nausea and vomiting; became comatose, and died 18 months after the onset of these symptoms.*

V. D., a 32-year-old white man, was admitted to the Presbyterian Hospital Sept. 5, 1940, in a comatose state. In 1931 he was hospitalized for "nervous breakdown." He was told at that time and again in 1937 that he had high blood pressure. Two and one-half years previously the patient was hospitalized for an attack of severe abdominal pain; he was cystoscoped and told he had "stones." No operation was performed. About one and one-half years before admission the patient first noted intermittent generalized muscle cramps, which became increasingly severe. He noted blurring of vision without headache for two months prior to admission. During the week preceding admission to another hospital, the patient developed nausea, vomiting, and generalized weakness. At this time the temperature was 97.2 F., pulse rate 86, respiration rate 24, blood pressure 110/90, and urine specific gravity 1.014; the sediment contained many white blood cells, and there was a trace of albumin. The hemoglobin was 8.3 gm.; the blood nonprotein nitrogen was 193 mg. per 100 ml., and the serum creatinine was 7.1 mg. per 100 ml. He received intravenous calcium, which relieved the muscle cramps, and a blood transfusion, but facial twitching was soon noted, and the patient lapsed into coma. Two days later he was transferred to the Presbyterian Hospital.

Physical examination on admission revealed a normal temperature, pulse rate, and respiratory rate. The blood pressure was 120/60. The patient was undernourished and comatose, and there was marked facial twitching. Narrowed arterioles, a few small exudates, and blurring of the optic nerve head were seen on funduscopic examination. The heart sounds were distant and of poor quality, although regular, and no murmur or friction rub was heard. The lungs were clear, and the abdomen was normal. There was no peripheral edema.

The urine specific gravity was 1.010, there was a trace of albumin, and many white blood cells but no red blood cells or casts were seen in the sediment. The blood urea nitrogen was 126 mg. per 100 ml., and the serum CO_2 was 7.3 mEq. per liter. A roentgenogram of the abdomen revealed no renal calculi, and the renal shadows appeared small.

The patient's temperature rose to 101 F.; he developed transient convulsions and died 48 hours after admission.

Autopsy.—The body was that of a thin young man. The heart was not enlarged. There were partially calcified plaques extending from the basal attachments of the aortic cusps toward the free margins. There was an extensive lobular pneumonia in the left lower lobe. The combined weight of the parathyroids was 1.145 gm. There was an encapsulated white nodule in the right inferior gland. The sternal marrow spaces contained little fat or red marrow and were filled with pale translucent material.

The right kidney weighed 140 gm.; the left, 110 gm. (Fig. 5). The capsule stripped with some difficulty, revealing an irregular surface. Several small cysts measuring from 1 to 3 mm. were scattered over the surface. On section the parenchyma had an unusual appearance. The medullary portion everywhere had a spongy composition due to the presence of innumerable tiny cysts separated by thin trabeculae. These cysts varied in diameter from less than 1 mm. to 3 to 4 mm. and extended out into the papillae of the pyramids. The cortex was irregular in

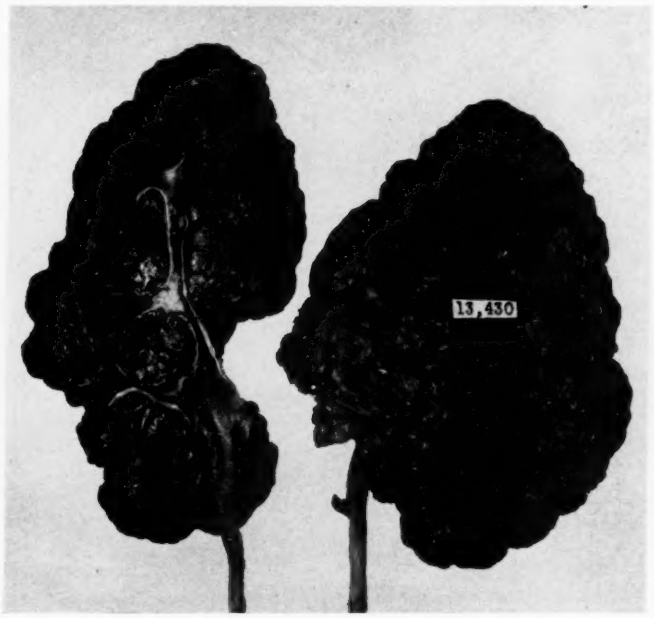

Fig. 5 (V. D.).—Small kidneys showing pyramids completely replaced by cysts and a very thin poorly demarcated cortex.

contour and was reduced in thickness to an average of 2 to 3 mm. No cortical striations were visible; the cut surface revealed scattered very small whitish translucent granules, some of which were soft, while others were hard and grated when scraped with a knife. The calices were enlarged, but the pelves and ureters were not dilated and were lined by smooth epithelium.

On microscopic examination all parathyroid glands showed marked clear cell hyperplasia and there was an encapsulated adenoma in the right inferior gland. There was extensive osteitis fibrosa.

The narrow renal cortex was composed of areas of atrophy and hypertrophy. In the atrophic areas there were completely hyalinzed glomeruli, atrophic tubules, and a few mononuclear inflammatory cells in the interstitial spaces. In other areas there were dilated tubules and enlarged glomeruli. Most of the glomeruli in these regions were delicate and but rarely adherent to the capsule. There was a zone of irregular cystic spaces which virtually replaced the entire medulla. These spaces were lined by low basophilic epithelium and filled with a variety of material. In some this was eosinophilic precipitated coagulum containing a few leucocytes. In other areas it consisted of laminated concretions, some of which were basophilic

and apparently calcified. Between these cysts was rather dense fibrous tissue and only occasional normal collecting tubules. There was mild intimal thickening and hyalinization of the arterioles.

The anatomical diagnoses were polycystic kidneys (medullary type), hyperplasia and adenoma of the parathyroids, osteitis fibrosa, and mild arteriosclerosis of coronary arteries.

CASE 4.—*A 15-year-old boy developed dyspnea and bowing of the legs two years before hospitalization. In the intervening period nervousness and muscle twitching were noted and dyspnea became more severe, and he died after being semicomatose for 24 hours.*

Q. R., a 15-year-old white boy, was admitted to The Johns Hopkins Hospital on Oct. 12, 1940, with the chief complaints of nervousness and delayed union of osteotomy of the left leg. He was well until two years before admission, at which time he developed dyspnea on exertion and bowing of the left leg and, later, some bowing of the right. One year later an osteotomy

Fig. 6 (Q. R.).—Photomicrograph of a large medullary cyst with surrounding atrophic parenchyma; × 16.

was performed to straighten the left leg. Bony union was so delayed that the final cast was not removed until 11 months later. Six months before admission the patient became increasingly nervous, and twitching of the muscles was noted. He had always consumed large amounts of water and suffered from enuresis until the age of eight. There was no history of hematuria, back pain, headaches, gastrointestinal distress, vomiting, or edema.

Physical examination revealed normal temperature, pulse rate 120, respiration rate 22, and blood pressure 128/78. The patient was a pale thin underdeveloped immature boy with a tremor of the hands and frequent twitching of the skeletal musculature. Chvostek's sign was positive. Funduscopic examination revealed slight dilatation of vessels and arteriovenous compression but no hemorrhages, exudates, or papilledema. The lungs were clear; there was a moderate tachycardia and a short apical systolic murmur. The abdomen was normal. There was thickening of costochondral junctions, a bowed right leg, and a tender healing left osteotomy. Unsustained ankle clonus was noted. There was no peripheral edema.

Laboratory findings were as follows: 3,350,000 red blood cells per cubic millimeter, hemoglobin 8.6 gm., hematocrit level 25%, and 5,250 white blood cells per cubic millimeter. The urine specific gravity was 1.012, with 1 + albumin and sediment containing occasional white blood cells and red blood cells but no casts. There was 3% excretion of phenolsulfonphthalein in two hours. The blood nonprotein nitrogen was 221 mg., the serum phosphorus 10.4 mg., and calcium 6.7 mg. per 100 ml. and sodium 134.3 mEq., CO_2 18.7 mEq., and chloride 98.6 mEq. per liter. The alkaline phosphatase was 14.8 Bodansky units. A roentgenogram of the left leg revealed a healing fracture of left tibia. Marked demineralization was noted.

The patient was given intravenous dextrose solutions, sodium bicarbonate, and a high-salt diet, and fluids were forced. The blood nonprotein nitrogen was 148 mg. per 100 ml. at the time of discharge, Oct. 19, 1940. He was admitted five months later, with increased pallor and weakness but little other change upon physical examination. Laboratory studies revealed 2,100,000 red blood cells per cubic millimeter; blood nonprotein nitrogen 250 mg., serum calcium 5.4 mg., and phosphorus 9.8 mg. per 100 ml., and CO_2 11.0 mEq. and chloride 104.6 mEq. per liter. The serum phosphorus rose to 13.4 mg. per 100 ml., and the patient appeared to be deteriorating rapidly. He developed hyperpnea and a terminal rise in blood pressure to 160 systolic and died after being semicomatose for 24 hours.

Autopsy.—The body was that of a thin young white boy. The details of examination of organs other than kidneys are unavailable.

The kidneys were approximately 50% normal size. The capsules stripped with ease, revealing a smooth cortex. On cut section the cortex and medulla were difficult to distinguish, but the cortex appeared narrower than usual. The pyramids, although not blunted, were small. Near the apices there were numerous smooth-walled cysts varying in diameter from approximately 1 mm. to 6 mm. The pelves and calices were neither dilated nor thickened.

Histologically, the renal parenchyma (Fig. 6) was the site of rather extensive diffuse atrophy, with some small irregular areas of lymphocytic infiltration. Most of the glomeruli were either hyalinized or hypertrophic. The ratio of hyalinized to normal and hypertrophic glomeruli was about 4:1. There was no thickening of the basement membranes. There was no crescent formation, and capsular adhesions were rare, but mild to moderate pericapsular thickening was frequently encountered. Many tubules were either normal or mildly dilated. However, in areas of marked atrophy they were very small and were frequently enclosed in thin hyaline rings. Many tubules contained small amounts of pale eosinophilic granular material. In the medulla there were numerous small cysts, up to 6 mm. in diameter. These were located chiefly in the pyramids near the apices, were lined by flattened epithelium, and contained only a few fragments of eosinophilic debris. Mild to moderate intimal thickening with hyalinization was present in many arterioles. The medium-sized arteries were unremarkable.

The anatomical diagnoses were polycystic kidneys (medullary type) and osteitis fibrosa.

COMMENT

In all these cases the outstanding clinical features were marked anemia and nitrogen retention, with only minimal retinal changes, without striking hypertension, without cardiac enlargement, and without convincing historical evidence of earlier symptoms and signs of chronic glomerulonephritis or recurrent pyelonephritis.

There are few references to similar cases in the foreign literature and only one in the English literature. Beitzke,[1] Markus,[2] and others have described the existence of medullary renal cysts. In 1913 Stammen [3] reported medullary cysts of the kidney in an 18-year-old boy, who apparently died, however, of cholangitis rather than in uremia; consequently this case is not included in our clinical discussion. A case of anemia and uremia reported in 1945 by Smith and Graham [4] appears to be similar in every respect to the four presented in this paper. The latter two cases are the only ones in which a detailed presentation of both pathological and clinical findings could be found. Recently, Jackson and his associates [5] have reported a case of a

25-year-old man with osteodystrophy and diabetes in association with "congenital polycystic hypoplasia of the kidneys." In this patient the cause of death was apparently insidious uremia and the clinical course was similar to those of our patients. However, from the pathological description it appears that cystic replacement of the pyramids, with surrounding cortical atrophy, did not occur in this case.

The pathological similarities in our four cases and the cases of Stammen and Smith and Graham are striking. The usual signs of nephritis were absent. There was no evidence of the primary glomerular lesions found in glomerulonephritis. It was more difficult to rule out healed pyelonephritis, although the usual stigmata of this disease were absent. There were no large irregular areas of scarring, "colloid casts," inflammatory exudates, or urinary tract obstructions. Also, it would be most unusual for pyelonephritis to cause the cystic replacement seen in the pyramids.

The vascular lesions were too mild to warrant consideration of the diagnosis of arteriolonephrosclerosis. Also, the presence of large numbers of atrophic glomeruli makes it unlikely that these represent cases of congenital hypoplasia. In contrast to the huge uniformly cystic kidneys of ordinary congenital polycystic disease, the kidneys in theses cases were small and the cysts were confined largely to the pyramids. It is possible, therefore, that these pathological findings represent an unusual type of congenital polycystic disease.

In analyzing these six cases the frequency of associated anomalies is of interest. In that reported by Stammen, cysts in the liver were found; in one of our cases (J. G.) there were cysts in the pancreas, stenosis of the renal arteries, and a clubfoot.

A discussion of the pathogenesis of this disorder is of necessity limited largely to speculation. Smith and Graham believed that the renal lesions were congenital and that progressive increase in the size of the cysts led to an "intrarenal hydronephrosis." The presence of large numbers of atrophic glomeruli in the absence of inflammatory changes certainly suggests compression of the cortex.

In the usual form of polycystic disease it has been accepted for many years that malunion of the metanephrogenic mesoderm and the metanephric diverticulum is responsible for cyst formation. Kampmeier [6] and McKenna and Kampmeier [7] demonstrated that early in fetal development the first three or four generations of tubules are temporary and persist for a short time as cystic structures. They have suggested that in polycystic kidney disease these structures may persist and grow into the huge cysts seen in adulthood. In recent years, question as to the validity of this theory has been raised by the work of Norris and Herman [8] and Lambert.[9] They have shown, using serial section reconstructions, that the cysts may occur in a random manner along the course of the nephron and that dysplastic alteration of tubule walls, occurring after fusion of the metanephrogenic anlage and the collecting ducts, may lead to cyst formation. Lambert has also shown, using inulin, that cysts may be part of functional nephrons. In one of our cases (S. M.) a cyst was seen to communicate with an otherwise normal tubule. It appears that in medullary cystic disease the cysts are probably formed in association with tubules. The location of the cysts is such that they could have arisen from the temporary cysts that are normally associated in fetal life with the first few generations of collecting tubules. Further elucidation of pathogenesis would require studies by microdissection techniques or serial section reconstruction.

Clinically, there were many similarities in all four cases presented and in the fifth case of Smith and Graham. (Stammen's case is not included in the clinical discussion because the patient did not die in uremia.) The deviation from the common clinical sequence in progressive renal failure was striking. In all cases uremia was insidious, often not detected until shortly before death. In all cases but one (J. G.) albuminuria was present in only "trace" or "1+" amounts. No casts or more than "occasional" red blood cells were noted in the urine of any of our patients or in the case of Smith and Graham. In four of the five the optic fundi were normal or near normal; in the fifth case (V. D.) occasional exudates were noted. A marked anemia was present in all instances. There was no history of hypertension except in Patient V. D., where the degree was unknown. None of the patients had significant hypertension on hospitalization. One of our cases (S. M.) had a preterminal blood pressure recording of 170/90, and there was a similar rise reported by Smith and Graham. In none of the cases was there a history of edema or any

Summary of Clinical Findings

Case	Age, Yr.	B. P.	Eye Grounds	Edema	Hemoglobin, Gm.	Urine Albumin	Sediment
V. D.	32	History of hypertension 120/60	Some exudate and slight blurring of nerve head	None	8.3	Trace	Many WBC; no RBC or casts
J. G.	28	140/80	Normal	None	8.0	+++	Few WBC; 0-2 RBC; no casts
S. M.	49	120/70 to 170/90 (terminal)	Normal	None	8.0	Neg. to trace Terminal ++	Occasional WBC; no RBC or casts
Q. R.	16	128/78	Slight A-V nicking	None	8.6	+	Occasional WBC and RBC; no casts
Smith and Graham	8	Terminal rise to 150/90	Normal	None	8.5	Faint trace	Negative

edema on physical examination, and none of the other symptoms and signs usually associated with chronic glomerulonephritis or recurrent pyelonephritis were present.

A summary of the clinical findings mentioned above is given in the Table. It may be noted that the patients vary in age from 8 to 49 years at the time of death, with one falling in each decade. This is in contrast to the usual pattern in polycystic disease, in which most of the mortalities occur in the first year of life or in the fourth or fifth decade.[10]

Although the number of cases presented is too small to warrant more than speculation, it may be that death in uremia due to medullary cystic disease of the kidney constitutes a clinical as well as a pathological entity. In the single adult patient with congenital hypoplasia of the kidneys described by Jackson and his associates the clinical course was similar to those seen in our cases, and it is possible that the same clinical syndrome exists in conjunction with this condition as well.

It is undoubtedly true that some patients dying of other types of renal disease, especially chronic pyelonephritis, may exhibit a clinical course similar to that seen in our patients. However, this clinical sequence is not seen universally in any other single disease entity and the pathological differences between medullary cystic disease and other end-stage nephritides seem unequivocal.

SUMMARY

Four cases of medullary cystic disease of the kidney terminating in uremia are presented. Two similar cases from the literature are discussed. In all cases the pathological findings are remarkably uniform. Small kidneys with numerous medullary cysts were observed. There was no evidence of a significant vascular or inflammatory component. The clinical findings in all cases are similar, consisting of insidious uremia and anemia alone, and are enough at variance with the usual clinical picture in progressive renal failure to suggest a clinical entity as well as a pathological one.

Drs. Homer Kesten and H. P. Smith gave suggestions and Dr. Warfield T. Longcope gave permission for the use of the case from his files.

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POLYMYXIN B THERAPY OF MENINGITIS FOLLOWING PROCEDURES ON CENTRAL NERVOUS SYSTEM

Beneficial Therapeutic Effect of Polymyxin B in Meningitis Due to Organisms of the Colon Group

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CINCINNATI

ONE PARTICULAR method whereby ordinarily noninvasive organisms of low virulence may produce clinical disease is their inadvertent introduction into various areas of the body during certain procedures. If the area is poorly controlled by host defences, the organism may flourish and frank infection may ensue. Thus, superficial infections of the urinary tract may result from contamination during instrumentation, and, similarly, meningitis may be produced by the injection of contaminated material into the cerebrospinal fluid. Meningitis due to Pseudomonas aeruginosa has followed simple lumbar puncture*; the injection of serum,[7] unsterile solutions of spinal anesthetics,† or antibiotics,‡ and pneumoencephalography,§ in which the air passed through a contaminated water trap. Infected craniospinal wounds, surgical and traumatic, have also resulted in Pseudomonas meningitis.‖ The mortality in untreated cases is substantial.

Recent success in treating Pseudomonas meningitis with polymyxin B¶ has prompted us to review five such cases, seen recently at the Cincinnati General Hospital and the Children's Hospital of Cincinnati, and one other case due to a similar organism. Each followed a procedure on the central nervous system, and the patients treated adequately with the proper antibiotic survived. The in vitro susceptibility of the organism responsible in each of five of the cases was determined by a tube dilution method [26] and is given in the Table. The organism from the remaining case (Case 4) was tested by a medicated disc method only, which is described in the case summary.

Read by title before the Central Society for Clinical Research, Chicago, Nov. 7 and 8, 1952.

From the Department of Medicine, University of Cincinnati College of Medicine and the Cincinnati General Hospital.

The antibiotics used in this study were provided as follows: chlortetracycline (Aureomycin) by Dr. Stanton M. Hardy, Lederle Laboratories Division, American Cyanamid Company; oxytetracycline (Terramycin) by Dr. Gladys Hobby, Chas. Pfizer & Company, Inc; polymyxin B (Aerosporin) by Dr. Donald S. Searle, Burroughs Wellcome & Company, Inc.

* References 1 through 5, and 6.

† References 8 through 15.

‡ References 16-18.

§ References 19 and 20.

‖ References 17, 21, and 22.

¶ References 15, and 23-25.

REPORT OF CASES

CASE 1.—M. B., CGH 282432 (Fig. 1), a 75-year-old white woman, was admitted to the surgical service of the Cincinnati General Hospital Jan. 26, 1952. Carcinoma of the colon was diagnosed, and on Feb. 4 a partial colectomy was performed. Anesthesia for this procedure consisted of the continuous instillation of procaine through a polyethylene catheter inserted into the subarachnoid space. A total of 350 mg. of procaine was used over a period of four hours and 10 minutes.

Following operation the patient was unusually lethargic, and the temperature rose to 102.2 F. She was placed on 300,000 units of penicillin and 1 gm. of streptomycin daily on Feb. 4. On Feb. 12 nuchal rigidity was detected, but the Kernig and Brudzinsky signs were negative. Lumbar puncture on Feb. 13 revealed grossly cloudy spinal fluid. The initial pressure was 180 mm. of water. The fluid contained 2,020 cells per cubic millimeter, all polymorphonuclear leucocytes. The protein was 300 mg., and the sugar 30 mg. per 100 cc. Culture of the spinal fluid was sterile. Three grams of oxytetracycline (Terramycin) per day was added to the therapy, with no detectable clinical improvement. The patient remained lethargic, and occasional twitches of the right arm and leg appeared. Paralysis on that side was noted Feb. 14. Lumbar puncture Feb. 15 revealed an initial pressure of 240 mm. of water. The fluid was again cloudy and contained 1,200 leucocytes. The sugar was 46 mg. per 100 cc. Culture of the fluid produced Ps. aeruginosa.

In Vitro Susceptibility of Bacteria Found in Five of the Cases *

Case	Streptomycin	Chlor-tetracycline	Oxytetra-cycline	Chlor-amphenicol	Polymyxin B
1	15.6	62.5	....	125	1.56
2	19.6	15.6	15.6	125	0.63
3	15.6	62.5	....	125	0.78
5	500	15.6	15.6	15.6	1.56
6	125	125	125	31.2	100

* Expressed as the minimum inhibiting concentration in gamma per cubic centimeter.

The patient continued to do poorly, and a final spinal tap was performed on Feb. 18. The initial pressure was 120 mm. of water. The fluid was cloudy, containing 1,800 cells, all polymorphonuclear leucocytes. The protein was 140 mg., the sugar 42 mg. per 100 cc. Smear revealed Gram-negative rods, and cultures of the fluid again produced Ps. aeruginosa. The patient died Feb. 20, 1952. Permission for autopsy was not obtained.

Comment.—That meningitis was induced by the spinal anesthesia in this case seems clear. Fever and lethargy were apparent immediately postoperatively and progressed over an eight-day period to signs of frank meningeal irritation. The course of the infection was uninfluenced by streptomycin, penicillin, and oxytetracycline therapy, and death occurred 16 days after the initial infection.

CASE 2.—I. B., CGH 93718 (Fig. 2), a 49-year-old Negro woman, was admitted to the orthopedic service of the Cincinnati General Hospital Nov. 27, 1951, complaining of progressive swelling of her right knee for five weeks. The patient had previously been hospitalized in 1949 for tuberculous peritonitis, which had been successfully treated with streptomycin.

Physical examination revealed a markedly swollen right knee, with limitation of motion and mild general tenderness over the area. The temperature was 103 F.

Laboratory studies showed the hemoglobin to be 11 gm.; the white blood cells numbered 9,850. The urine was not remarkable. Lumbar puncture on Nov. 28 yielded clear fluid containing no cells. The cerebrospinal fluid sugar was 52 mg. per 100 cc.

On Dec. 6, 1951, biopsy of the joint was performed under spinal anesthesia. One hundred milligrams of procaine was administered through a lumbar needle in a single injection. After this procedure the temperature remained elevated, but the cause of the fever could not be ascertained.

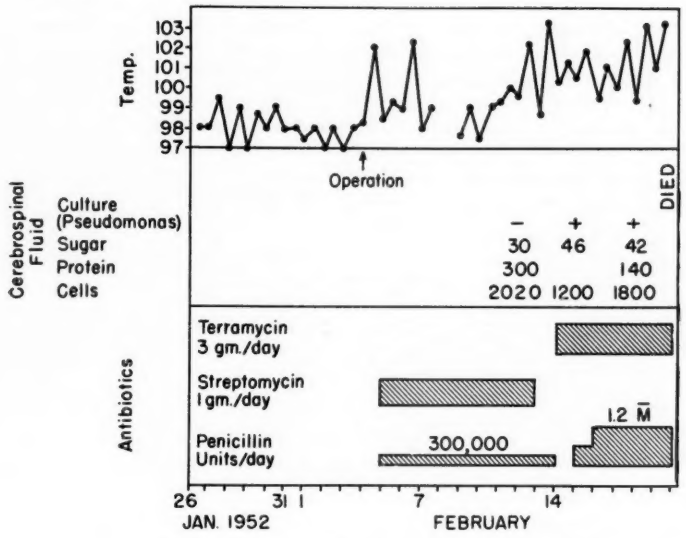

Fig. 1 (Case 1).—Summary of clinical and laboratory data.

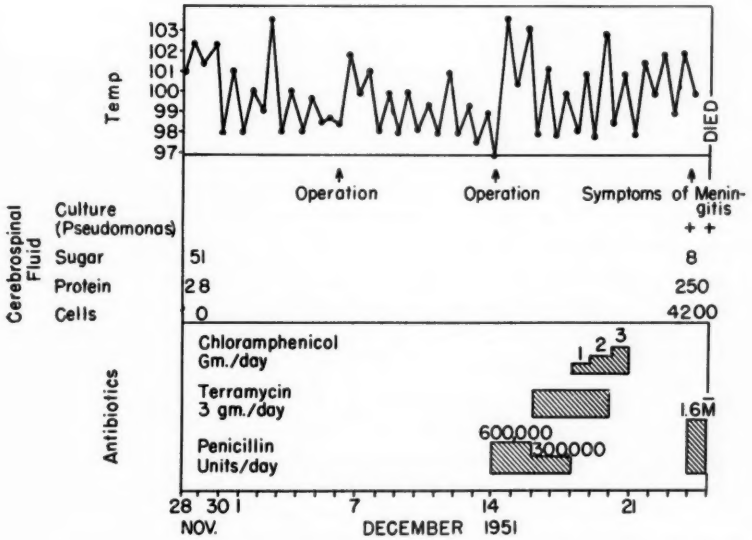

Fig. 2 (Case 2).—Summary of clinical and laboratory data.

On Dec. 14 sudden massive hemorrhage occurred at the earlier operative site. The previous surgical wound was explored, and the bleeding vessel was ligated. Procaine was employed as spinal anesthesia through an indwelling lumbar subarachnoid polyethylene catheter over a period of 2 hours 15 minutes. The postoperative course was uneventful until Dec. 16, when the temperature rose to 105 F. Physical examination on Dec. 23 revealed sinus tachycardia but no stiffness of the neck. On Dec. 24 the patient complained of paresis of the right arm and general weakness and seemed to be more lethargic. The neck at this time resisted anterior flexion; neurological examination otherwise was normal. Lumbar puncture revealed an initial pressure of 204 mm. of water. The fluid was cloudy, containing 4,200 WBC, 92% of which were polymorphonuclear leucocytes and 8% lymphocytes. The protein was 250 mg., the sugar 8 mg. per 100 cc., and culture of the cerebrospinal fluid produced Ps. aeruginosa.

The patient was placed on treatment with penicillin, 600,000 units per day, and oxytetracycline, 3 gm. per day, intravenously. Her condition deteriorated rapidly, and chloramphenicol, streptomycin, and sulfadiazine were added. She died Dec. 25, 1951.

Spinal fluid obtained on the day of death again contained Pseudomonas on culture. Permission for autopsy was not obtained.

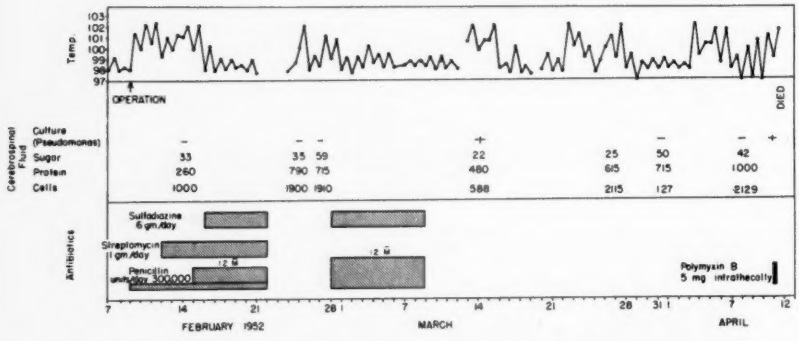

Fig. 3 (Case 3).—Summary of clinical and laboratory data.

Comment.—Meningitis could have arisen from the lumbar puncture on admission or, more likely, from either of the spinal anesthetics. Penicillin and oxytetracycline, given concurrently, were of no avail.

CASE 3.—I. K., CGH 266973 (Fig. 3), a 62-year-old white man, was admitted to the surgical service of the Cincinnati General Hospital Feb. 5, 1952, for repair of ventral hernia.

Physical examination revealed a well-developed, somewhat obese man. The neck was supple. The blood pressure was 162/86. The heart was not enlarged; the lungs were clear. A large ventral hernia was present.

Laboratory studies revealed the hemoglobin to be 14 gm. per 100 cc. The white cells were 7,200. The urine was not remarkable.

On Feb. 9 the hernia was repaired. Anesthesia was provided through the continuous spinal administration of procaine and tetracaine (Pontocaine) over a period of two hours.

Postoperatively the temperature rose as high as 102 F., and on Feb. 12 the white cell count was 11,650. The patient was given penicillin, 300,000 units daily, postoperatively, and on Feb. 11 1 gm. of streptomycin daily was added. At this time the patient complained of headache, and on Feb. 14 lumbar puncture was performed. The initial pressure was 88 mm. of water, and 10 cc. of turbid spinal fluid was removed. This contained 1,000 WBC, of which 96% were polymorphonuclear leucocytes. The protein was 260 mg., and the sugar 33 mg. per 100 cc. Smear and culture were negative for pathogens. Penicillin dosage was increased to 1,200,000 units daily at this time, and on the next day sulfadiazine, 6 gm. daily, was added.

The patient continued to complain of headache, and on Feb. 17 hiccough developed, which continued for four days. By Feb. 21 the temperature had fallen to normal and antibiotics were discontinued.

On Feb. 25 the temperature rose to 102 F. and lumbar puncture was repeated. Fluid contained 1,900 WBC, 98% of which were polymorphonuclear leucocytes. The protein was 790 mg., and the sugar 35 mg., per 100 cc. Culture was sterile, and smear was negative for pathogens. At this time stiffness of the neck could be elicited.

Penicillin was again begun on Feb. 28, in doses of 12,000,000 units daily, with sulfadiazine, 6 gm. daily. On this regimen the patient felt better but continued to run a low-grade fever, the temperature at times reaching 101 F. Penicillin and sulfadiazine were discontinued March 9, with little change in the clinical status subsequently.

A positive spinal fluid culture for Ps. aeruginosa was obtained on March 14. This fluid was xanthochromic and turbid and contained 588 WBC, 80% of which were polymorphonuclear leucocytes. The protein was 480 mg., the sugar 22 mg., per 100 cc.

The patient continued to be relatively asymptomatic and appeared to be losing little, if any, ground. However, on April 9 he became acutely ill, with increased lethargy and incontinence of urine. Although sensitivity of the organism to polymyxin B had not been determined at this time, it was decided to try this drug, in view of the patient's increasingly critical condition. Five milligrams of polymyxin B was given intrathecally on April 11, in 10 cc. of saline. The patient grew steadily worse, and died quietly the next day.

Autopsy.—Examination was performed two and one-half hours after death.

The brain weighed 1,375 gm. There was marked congestion and edema, with flattening of the gyri and obliteration of the sulci. Much grayish and yellowish white exudate was present in the sulci throughout, being most marked over the anterior aspects of the frontal lobes and laterally over the cerebellum. In these areas the exudate was 2 to 4 mm. thick and was adherent and tenacious.

Exudation was present also over the cord, which was removed *in toto*. The paranasal sinuses and the chambers within the petrous bones showed no inflammation or exudate.

Section of the brain after fixation in 10% formalin revealed exudation, approximately 1 mm. thick, lining the ependyma of all ventricles.

Cultures of the arachnoid exudate were taken at the time of autopsy, revealing Pseudomonas and staphylococci. The blood culture was negative.

Microscopic examination of the brain and cord revealed generalized dense leptomeningitis, varying from an acute purulent process to early organization. Organization was more marked about the cord, where collagen was at times noted. The small arteries were not involved; occasional perivenous infiltration was present.

Also present were bronchiectasis, lobular pneumonia, pulmonary edema, myocardial fibrosis and hypertrophy, generalized arteriosclerosis, and chronic pyelonephritis.

Comment.—This case illustrates the difficulty occasionally encountered in obtaining positive cultures in this condition, for, while frank meningitis was present over a two-month period, only one of six cerebrospinal fluid cultures was positive. The effect of chemotherapy in this case was equivocal at best. Had polymyxin been given earlier, the patient might have survived.

CASE 4.—J. L., CH 72707 (Fig. 4), a 2-year-old white boy, was admitted to the Cincinnati General Hospital for excision of a large lumbar meningocele. Operation was performed on June 25, 1950, under general anesthesia.

Postoperatively, at the Children's Hospital, the patient received 300,000 units of penicillin daily. The wound continued to drain spinal fluid for a few days, and temperatures as high as 101 F. were noted. On the fourth postoperative day bladder distention was observed and a retention catheter was inserted. On July 8 the wound again began draining, and the temperature rose to 104 F. At this time stiffness of the neck and a positive Kernig sign were observed.

On July 9 a purulent discharge, which was thought to be spinal fluid, was seen to issue from the wound. This contained 80,000 WBC, of which practically all were polymorphonuclear leuco-

cytes. The sugar level was too low to measure, and culture of the spinal fluid produced Ps. aeruginosa. Penicillin dosage was increased to 600,000 units daily. Chlortetracycline (Aureomycin), 750 mg. daily, and sulfisoxazole (Gantrisin), 4 gm. daily, were added.

The temperature continued to be elevated, and signs of meningeal irritation did not subside. By July 28 the surgical wound was healed, and penicillin and sulfisoxazole were discontinued. A lumbar puncture, on Aug. 4, revealed opalescent fluid containing 1,300 WBC, 95% of which were polymorphonuclear leucocytes. The protein was 23 mg., the sugar 20 mg. per 100 cc., and culture again produced Ps. aeruginosa. At this time chloramphenicol, 600 mg. daily, was given by mouth.

On August 18 chlortetracycline was discontinued. Chloramphenicol was continued, and to it were added streptomycin, 0.5 gm. intramuscularly and 50 mg. intrathecally daily. The patient showed no clinical response, and on Aug. 28 Pseudomonas was still present in the spinal fluid. Streptomycin was stopped.

The organism was tested at the Children's Hospital for sensitivity to various antibiotics, using the medicated disc method, and it was found to be resistant to sulfadiazine, streptomycin,

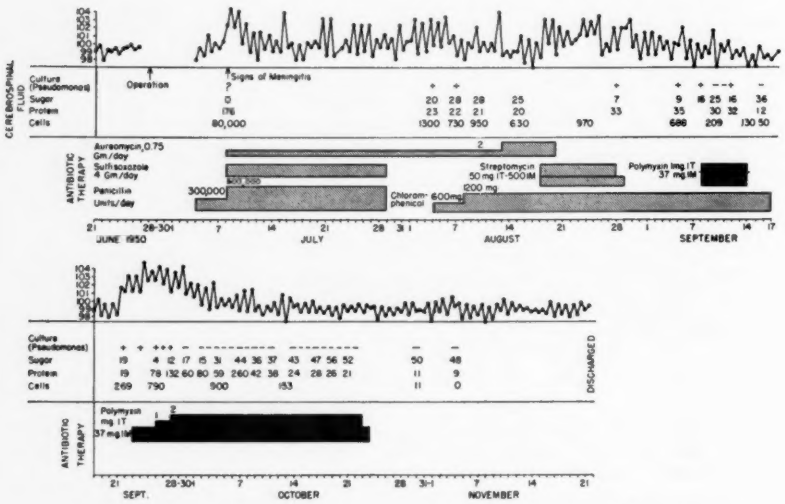

Fig. 4 (Case 4).—Summary of clinical and laboratory data.

chlortetracycline, chloramphenicol, oxytetracycline, and bacitracin. Tests using polymyxin B suggested sensitivity of the organism to concentrations obtainable with intrathecal injections, inasmuch as a 12.6 mm. disc impregnated with as little as 10 γ per cubic centimeter of polymyxin B produced a zone of inhibition of 18 mm. On Sept. 8 the fluid was still positive for Pseudomonas. On this day 1 mg. of polymyxin B was given intrathecally and 37 mg. intramuscularly. Both doses were repeated daily for a total of six days. A culture was positive on Sept. 12, but cultures obtained on September 9, 10, and 11 were negative.

During the time that polymyxin B was given the patient was irritable and anorexic and he slept poorly. His temperature, however, fell to normal, and several days after polymyxin had been discontinued these symptoms disappeared. On Sept. 19 chloramphenicol (Chloromycetin) therapy was stopped. The spinal fluid on Sept. 16 was sterile, and the patient's general condition improved considerably.

On Sept. 21 his temperature rose, and on the next day the spinal fluid was again positive for Pseudomonas. Polymyxin B, 37 mg. daily, given intramuscularly, was begun on Sept. 23. On Sept. 24 the spinal fluid culture was positive. On Sept. 26 and 27 1 mg. was given intrathe-

cally; on Sept. 28 the daily dose was raised to 2 mg. and was continued for 25 days. On Sept. 28 the culture was positive, but it was negative on Sept. 30 and thereafter. The temperature slowly fell to normal again, and the spinal fluid gradually returned to normal also.

The patient was discharged Nov. 22, 1950, with a normal spinal fluid. He has been seen in the clinic from time to time and has shown no subsequent evidence of meningitis.

Comment.—This case illustrates the efficacy of polymyxin B in a persistent infection of the meninges which resisted treatment with a number of other antibiotics. The effect of the drug was prompt and, after the initial inadequate course, was permanent.

CASE 5.—E. C., CGH 285487 (Fig. 5), a 47-year-old Negro man, was admitted to the Cincinnati General Hospital May 12, 1952. A diagnosis of miliary and meningeal tuberculosis was made.

Laboratory studies revealed 13.5 gm. of hemoglobin per 100 cc., 4,500,000 red blood cells, and 3,600 white blood cells, of which 55% were polymorphonuclear leucocytes, 38% lymphocytes, 6% monocytes, and 1% eosinophiles. The corrected sedimentation rate (Wintrobe) was 37 mm. in one hour. Urinalysis was normal. The spinal fluid pressure in the lumbar space was 120

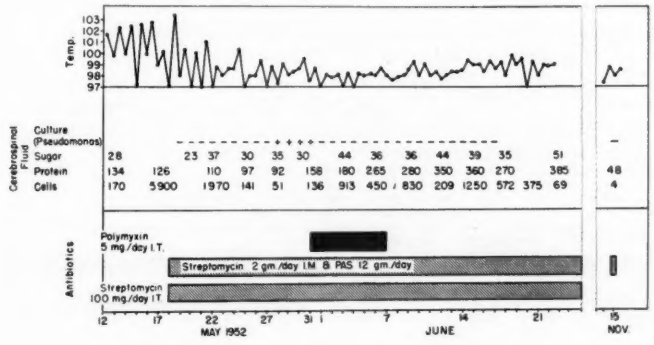

Fig. 5 (Case 5).—Summary of clinical and laboratory data.

mm. The fluid was clear but contained 170 lymphocytes. The cerebrospinal fluid protein was 134 mg. and the sugar 28 mg. per 100 cc. A smear of the cerebrospinal fluid demonstrated acid-fast bacilli, and guinea pig inoculation subsequently revealed tuberculosis. The chest roentgenogram on admission showed diffuse miliary densities.

The patient was placed on streptomycin, 2 gm. daily, and *p*-aminosalicylic acid, 12 gm. daily. A small polyvinyl catheter was inserted in the lumbar subarachnoid space. One hundred milligrams of streptomycin was instilled through this catheter daily after the removal of fluid for studies.

In spite of strict aseptic procedure, routine cultures, which had been obtained daily, produced Ps. aeruginosa on the 15th through the 20th hospital days.

On the 20th hospital day 5 mg. of polymyxin was added to the daily dose of intrathecal streptomycin, and eight consecutive daily doses were given. Cultures for Pseudomonas became negative on the 21st day and remained negative thereafter. No detectable side-effects of polymyxin were noted. The patient has remained under observation for 14 months and is well.

Comment.—An early diagnosis no doubt contributed to this patient's recovery. The absence of fever or an increase in the pleocytosis and the slight increase in the cerebrospinal fluid protein may also be attributed to this. Cultures were promptly sterilized when polymyxin B was given intrathecally.

CASE 6.—L. F., CGH 206262 (Fig. 6), a 30-year-old Negro housewife, entered the Cincinnati General Hospital May 15, 1952, because of severe headache, vomiting, and loss of consciousness. Physical examination revealed a temperature of 99.6 F., pulse rate of 60, and blood pressure of 180/100. She was drowsy, and the neck was moderately resistant to anterior flexion. Laboratory work revealed the hemoglobin to be 13 gm. per 100 cc., and WBC 22,700, 88% of which were polymorphonuclear cells and 12% lymphocytes. Urinalysis, Kahn test, and chest and skull x-rays were negative. Lumbar puncture revealed bloody fluid under a pressure of 180 mm. of water; chemical and bacteriological studies were not done. A cerebral angiogram was obtained on May 26, revealing a nonvascular mass in the left temporal lobe.

On May 27 the patient became comatose, with a right hemiplegia. Lumbar puncture again revealed bloody fluid, with 260 mg. of protein and 62 mg. of sugar per 100 cc. Penicillin and sulfadiazine were begun at this time. On June 4 the left temporal lobe was explored and a hematoma was evacuated, revealing anomalous vascular formations in the middle cerebral artery. A polyethylene catheter was inserted into the lumbar subarachnoid space at this time for postoperative decompression.

Postoperatively the patient improved but continued to show a low-grade fever. Streptomycin was started, and sulfadiazine was stopped.

By June 10 the catheter had not been used, and it was removed. The pressure at this time was 110 mm. of water, and the fluid was described as clear. On the next day the temperature

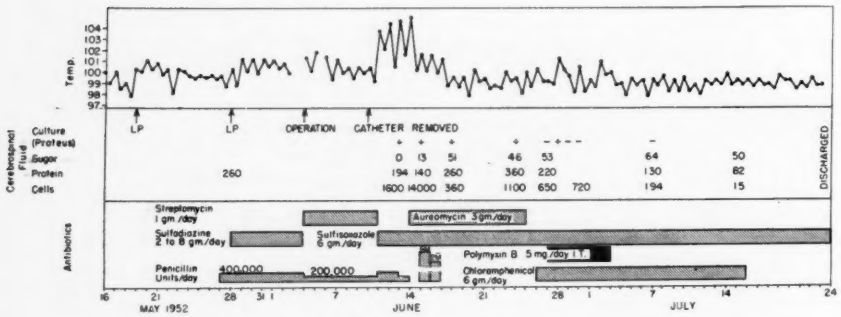

Fig. 6 (Case 6).—Summary of clinical and laboratory data.

rose suddenly to 103.6 F. Although urinalysis was normal, a urinary tract infection was suspected, and sulfisoxazole (Gantrisin) was started and streptomycin stopped. On June 13 the white cell count was 15,200 and a blood culture was sterile. Lumbar puncture revealed turbid fluid, with a pressure of 260 mm. of water and containing 1,600 cells, all of which were polymorphonuclear. The protein was 194 mg. per 100 cc., and the sugar was too low to measure. Culture produced a Gram-negative rod, subsequently identified as Proteus rettgeri.#

The next day the patient was again comatose. Lumbar puncture then revealed a pressure of 460 mm. of water, and on removal of 18 cc. of turbid fluid the patient regained consciousness. Ten thousand units of penicillin in 10 cc. of saline was given intrathecally, and chlortetracycline, 3 gm. daily, was started orally. Penicillin was again injected on June 15, at which time the culture was again positive for P. rettgeri.

In spite of the meningitis, the patient's general condition remained fairly good. Stiffness of the neck was intermittently present, and by June 18 the temperature had fallen to less than 100 F.

It was found that the organism isolated from the spinal fluid was resistant to streptomycin, chlortetracycline, oxytetracycline, and polymyxin B (Table). The growth of the organism was inhibited, however, by 31.2 γ of chloramphenicol per cubic centimeter. In order to detect any possible synergism between pairs of these antibiotics, a modification of the technique of Jawetz [27]

Dr. Charles C. Croft, Department of Health, State of Ohio, Columbus, Ohio, and Dr. John M. Slack, University of West Virginia School of Medicine, provided the ultimate identification of this organism.

was employed. Tubes of broth were set up containing each of the following antibiotic concentrations singly and in pairs, so that all combinations of two were represented:

Streptomycin	10 γ/cc.
Chloramphenicol	20 γ/cc.
Chlortetracycline	5 γ/cc.
Oxytetracycline	5 γ/cc.
Polymyxin B	10 γ/cc.
Sulfadiazine	15 mg./100 cc.

All tubes except those containing chloramphenicol showed grossly progressive growth over an eight-hour period. This growth was not visibly different from that of a control without antibiotics. All tubes containing chloramphenicol were sampled at the end of six hours. The greatest difference from that of chloramphenicol alone was seen in the chloramphenicol and polymyxin B tube, in which the colony count was decreased one-hundred-fold from that of chloramphenicol alone.

While it is doubtful whether this represents a significant degree of antibiotic synergism, the patient was, nevertheless, started on a combination of chloramphenicol and polymyxin B. On June 26 chloramphenicol, 6 gm. daily, was started, and on the next day 5 mg. of polymyxin B was injected intrathecally in 10 cc. of saline. This was repeated daily for a total of six days. Spinal fluid culture became negative on June 27, at the time of the first polymyxin injection, and on June 29 and 30. One positive culture was obtained June 28. While considerable distress was induced by the tapping procedure, no detectable toxicity or pain was caused by the polymyxin B. Temperature rises to 101 F. were noted, the levels returning to normal after the end of intrathecal therapy.

Lumbar puncture, on July 15, revealed normal pressure and clear fluid, containing 15 cells per cubic millimeter. The protein was 82 mg., and the sugar 50 mg. per 100 cc. Chloramphenicol was stopped on the next day, and the patient was transferred to another institution for care of her neurologic residuals. During the 12 months after discharge there has been no recurrence of the meningitis.

Comment.—The role of polymyxin B in curing this patient was probably insignificant, since the sensitivity of chloramphenicol suggested that it might have been of use in this regard and since the culture was sterile even before polymyxin was started.

COMMENT

Why it should be that Pseudomonas so frequently is the contaminating organism in such cases as these is at least in part explained by its unusual hardiness and adaptability to adverse conditions. It is ubiquitous as a skin saprophyte and is commonly found about the hospital ward.

A comprehensive review of meningitis due to Pseudomonas has been made by Stanley,[28] including the literature through 1945. Numerous reports have appeared since. Harris, Buxbaum, and Appelbaum [18] reported four cases of pneumococcal meningitis in which Pseudomonas infection supervened from the use of contaminated syringes employed in mixing penicillin that was injected intrathecally. The same contaminated solution given intramuscularly did not produce abscesses. Two patients survived after treatment with sulfadiazine.

Streptomycin has been used with success in the treatment of some patients. The initial attempts of Cairns, Duthie, and Smith [29] to use streptomycin intrathecally were not encouraging in three cases of Pseudomonas meningitis. All were advanced cases, however, and systemic streptomycin was not given. Paine, Murray, Seeler, and Finland [30] treated three patients with intramuscular and intrathecal streptomycin and were able to cure two. Merwarth, Rosenberg, and Pulito [13] observed a case following spinal anesthesia and cured the patient with streptomycin

and sulfadiazine. Keefer and Hewitt collected 11 cases of Pseudomonas meningitis treated with streptomycin.[31] Seven occurred after lumbar puncture for diagnostic purposes, for injection of penicillin, or for spinal anesthesia. Six of the 11 patients survived. Pastor, Gefter, and Baer [15] described two cases of Pseudomonas meningitis following spinal anesthesia. Both patients were cured with streptomycin intramuscularly and intrathecally. A combination of chlortetracycline and streptomycin was used successfully by Ginsberg and Hyman [32] in one case.

The survival rate of Pseudomonas meningitis before the use of streptomycin cannot be fairly assessed, owing to the natural tendency to report therapeutic successes only. Thus, by collecting all reported cases, Stanley was able to show a survival rate of 55% before streptomycin. Keefer and Hewitt's 11 patients [31] receiving streptomycin, on the other hand, were apparently unselected as regards the outcome, and their survival rate seems to indicate therapeutic progress.

Of the newer antibiotics, only polymyxin B has shown real promise against Pseudomonas infections. Schoenbach [23] mentioned three cases in which polymyxin B was used intrathecally. He found that the drug does not pass into the subarachnoid space, even in the presence of meningitis, but that intrathecal injections produce prolonged concentrations in the spinal fluid. Hayes and Yow,[14] Yow,[33] and Tomlin [24] have reported additional cases, all with survival. These patients received polymyxin B both intramuscularly and intrathecally.

Jawetz [25] has emphasized that intramuscular polymyxin need not be given when the intrathecal route is used, and, like Schoenbach, he obtained good results in two cases with intrathecal medication only.

Other antibiotics used include neomycin, which was used successfully by Ditowski, Goldman, and Goldin [34] and by Knight, Hardy, and Negrin.[35] Of interest is the use of streptokinase-streptodornase in the case of the latter. This has also been reported by Tillett, for a patient also receiving sulfadiazine and streptomycin intramuscularly only.[36] Distinct benefit seems to have been obtained with the use of the enzyme in at least one of these cases.

Particularly in our fourth and fifth cases is the failure of other commonly used antibiotics contrasted with the rapid eradication of infection by the use of polymyxin. In both, the spinal fluid cultures became negative within 24 hours after adequate doses of intrathecal medication were given. This is in contrast to the previous experience in treating Pseudomonas meningitis with sulfadiazine and streptomycin, in which improvement, when it occurred, was slow and in which spinal fluid cultures were slow in converting.

SUMMARY

The courses in three cases of meningitis due to Pseudomonas aeruginosa secondary to a procedure upon the central nervous system are described. The fatal outcome following treatment with ineffective antibiotics is demonstrated.

Two additional cases are described in which treatment with polymyxin B was successful, as well as another due to a Proteus species, in which chloramphenicol plus polymyxin effected a cure.

The effectiveness of polymyxin when given by the intrathecal route is demonstrated.

Permission to include Case 5 was given by Dr. Merlin Cooper, of the Children's Hospital. Mrs. Jean Donnelly and Miss Judith Carleton gave technical assistance.

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HEPATITIS OF MALARIAL ORIGIN

Clinical and Pathologic Study of Fifty-Four Korean Veterans

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HEPATITIS is the most significant feature of malaria now that drugs capable of eradicating the parasite from the body have been developed. Rapid present-day therapeutic measures fail to take cognizance of the fact that the hepatitis may be more incapacitating than the acute episode of parasitemia.

Malaria has been found in 6.6% of returning Korea veterans.[1] Early in our experience with these patients we were impressed with the high incidence of abnormal hepatic function. The literature was reviewed, and numerous references concerning liver disease in malaria were found.* Most of these referred to hepatic dysfunction complicating malarial fever therapy of tertiary syphilis.

Lippincott and co-workers reported transient abnormal hepatic function in 317 cases of chronic relapsing Plasmodium vivax malaria. Other authors investigating hepatic dysfunction in malaria either did not perform extensive tests of liver function or did not obtain liver biopsy specimens.

MATERIALS AND METHODS

Fifty-four Korea veterans with malaria were studied between June, 1951, and December, 1952. Liver-function tests were performed on 52, and liver biopsy specimens were obtained from 34. All had been in Korea from 3 to 12 months and had been on chloroquine suppressive therapy. The interval between cessation of suppressive therapy and onset of symptoms of malaria varied from 2 weeks to 12 months, with an average of 7 months.

Hepatic involvement was evaluated by means of history and physical examination, serial liver-function tests, peritoneoscopy, and liver biopsy by means of the peritoneoscope forceps. Subsequent biopsy specimens were obtained four weeks after conclusion of antimalarial therapy from 25 patients. Liver-function tests were performed at the time of admission and weekly thereafter. They included determination of total and fractional serum proteins, cephalin-cholesterol flocculation, thymol turbidity, cholesterol and cholesterol esters, alkaline phosphatase, sulfobromophthalein (Bromsulfalein) excretion, and direct-reacting and total serum bilirubin.

No therapy was started during the acute attack until the parasite had been demonstrated, the first battery of liver-function tests obtained, and peritoneoscopy with liver biopsy performed. Therapy consisted of chloroquine (chloroquine diphosphate 1.0 gm., followed by 0.5 gm. in six hours, 0.5 gm. daily for four days, and then 0.5 gm. weekly for six weeks) in 37 of the patients

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Sponsored by the Veterans Administration with the approval of the Chief Medical Director. Statements and conclusions by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

* References 2-19.

and pentaquine and quinine (pentaquine phosphate 20 mg. three times daily, with quinine, 0.6 gm. three times daily for two weeks) in 17 patients. The patients were kept at bed rest on a high-protein high-calorie medium-fat diet with vitamin supplement (Theragran, Squibb). The regimen of therapy was the same as that used for acute infectious hepatitis. It was continued until the patient was asymptomatic and the liver-function tests were approaching normal.

RESULTS

All 54 patients were infected with the P. vivax protozoan, and one infection was mixed with Plasmodium malariae. The average age of the patients was 23.9 years.

Results of liver-function tests were abnormal in the 52 patients so studied. The range of abnormality was broad, varying from slight elevation of the cephalin-cholesterol flocculation and thymol turbidity to abnormalities of all components of the liver profile. The four most common abnormalities were found in the cephalin-cholesterol flocculation, thymol turbidity, sulfobromophthalein excretion, and cholesterol-cholesterol ester ratio. Generally, the most marked abnormalities occurred during the second and third weeks, after which liver function rapidly reverted

TABLE 1.—*Incidence of Liver-Function-Test Abnormalities in Acute Malaria* *

Liver-Function Test	Patients Examined, No.	Abnormal Tests, No.	% Abnormal
Cephalin flocculation	51	49	96.0
Thymol turbidity	51	44	86.2
Sulfobromophthalein excretion	47	35	74.4
Cholesterol	49	35	71.4
Cholesterol esters	49	26	53.0
Albumin/globulin ratio	45	23	51.1
Serum bilirubin, total	52	20	38.4
Alkaline phosphatase	37	6	16.2
Total protein	50	8	16.0

* Total patients in series, 54; total patients examined by liver-function tests, 52.

toward normal. Table 1 shows the liver-function test, the per cent of patients on whom the test was performed, and the per cent of abnormal findings. Table 2 shows liver-function-test results in 33 patients on admission and four weeks after completion of therapy. At the four-week follow-up minor degrees of liver-function-test abnormalities remained in 22 of them, although they had been asymptomatic for over a month. In all instances results of liver-function tests showed definite improvement.

A liver biopsy specimen was obtained in 34 cases (62.0%). In 31 instances (91.9%) the liver was abnormal, either by gross or microscopic evaluation. In six patients the liver appeared normal on peritoneoscopic visualization but the biopsy revealed microscopic changes; however, in only two was the liver histology normal when gross abnormalities were present. Twenty-three patients (67.7%) had both gross and microscopic liver changes (Table 3).

The gross appearance of the liver in association with malaria is as follows [20]: There is slight to moderate enlargement of both lobes. The inferior edge is somewhat blunted, and the color is lighter than normal. Typical microscopic alterations include increased Kupffer cell activity, swelling of liver cells, compression of sinusoids, clumping and opacification of cytoplasm of hepatic cells, decreased glycogen content, marked variation in size and staining quality of nuclei, and numerous mitoses of liver cells (Fig. 1). In addition there is an infiltration of the sinusoids by

TABLE 2.—*Results of Liver-Function Tests in Acute Malaria on Admission to the Hospital and Four Weeks After Completion of Treatment* *

Case	BSP Retention, 45 Min.		Total Protein		A/G Ratio		Serum Bilirubin				Cephalin-Cholesterol Flocculation				Thymol Turbidity		Cholesterol (Blood)		Cholesterol Esters (Plasma)		Alkaline Phosphatase (Bodansky)	
							B		A		B		A									
	B †	A †	B	A	B	A	Dir.	Tot.	Dir.	Tot.	24 Hr.	48 Hr.	24 Hr.	48 Hr.	B	A	B	A	B	A	B	A
1.	7.2	5.0	6.5	7.0	4.6/1.9	4.8/2.2	0.3	1.0	0.4	0.9	2+	4+	2+	2+	6.0	3.2	173	202	59	95	2.0	3.0
2.	12.4	2.0	7.8	6.8	5.5/2.3	5.3/1.5	0	0.5	0.4	0.9	3+	4+	0	1+	6.4	4.6	208	198	55	137	3.1	2.7
3.	7.0	6.0	7.2	6.5	4.8/1.4	4.8/1.7	0.2	1.6	0.4	0.9	2+	4+	1+	4+	9.7	4.0	162	254	47	157	2.2	2.4
4.	11.2	4.2	6.8	7.0	5.1/1.7	5.2/1.8	0.3	1.2	0.3	0.7	2+	4+	0	0	5.0	2.9	223	158	103	96	6.0	3.8
5.	10.0	4.0	6.5	6.6	3.8/2.7	4.4/2.1	0.3	0.9	0.3	0.8	2+	3+	2+	3+	5.1	4.2	157	221	71	98	2.3	3.1
6.	9.0	2.4	7.8	7.6	4.6/3.2	5.0/2.6	0.7	1.5	0.6	1.5	2+	3+	0	1+	7.2	5.1	152	170	59	101	2.7	3.3
7.	6.0	2.5	6.0	6.9	4.1/1.9	4.8/2.1	0.5	1.2	0.6	1.3	2+	3+	0	1+	2.5	5.1	142	173	64	106	2.4	2.9
8.	49.1	4.0	7.6	7.7	4.7/2.9	5.3/2.4	0.5	1.8	0.2	0.7	2+	3+	0	0	5.9	3.8	208	222	68	136	4.6	3.2
9.	36.0	4.0	6.9	7.6	4.6/2.3	5.0/2.6	0.2	1.0	0.3	0.7	2+	3+	1+	4+	2.7	5.4	168	220	66	137	5.5	4.0
10.	10.0	4.0	5.8	9.0	4.4/1.4	6.2/2.8	0.3	1.4	0.1	0.3	2+	4+	0	1+	10.0	8.0	127	257	92	170	3.8	3.3
11.	10.0	3.5	6.4	6.7	3.9/2.8	4.7/2.0	0.3	1.3	0	0.6	2+	4+	0	0	5.3	1.3	173	206	101	137	3.1	3.3
12.	10.0	3.4	7.8	7.3	4.9/2.9	5.2/2.1	0.3	1.3	0.3	0.3	2+	4+	0	0	2.3	2.1	142	210	93	140	2.7	2.9
13.	8.0	8.0	6.5	7.3	4.5/2.0	5.1/2.2	0.5	0.9	0.4	0.4	2+	3+	0	1+	2.9	2.1	143	221	95	135	3.1	1.7
14.	8.0	2.5	6.7	7.5	3.9/2.8	3.8/1.9	0.4	1.0	0.3	0.5	2+	3+	0	0	7.0	2.4	131	351	86	210	3.0	3.0
15.	10.0	4.6	7.3	6.9	4.9/2.4	4.7/2.2	0.4	1.1	0.2	0.3	2+	3+	0	1+	5.1	3.6	222	235	135	153	1.6	1.4
16.	13.6	4.5	7.6	6.2	4.7/2.9	4.5/1.7	0.4	0.9	0.1	0.5	2+	4+	0	0	5.1	2.4	109	182	73	124	2.6	1.8
17.	11.5	4.0	6.0	6.4	4.1/1.9	4.5/1.9	0.3	0.8	0.4	0.8	3+	4+	0	2+	6.0	2.1	142	221	83	133	2.4	2.9
18.	8.3	2.0	7.3	7.1	2.4/2.9	5.1/2.0	0.5	1.0	0.5	0.9	3+	4+	0	0	5.2	1.6	186	220	104	136	4.5	2.3
19.	8.3	4.0	7.3	7.8	4.7/2.6	5.0/2.8	0.4	0.9	0.4	0.7	0	0	0	1+	5.8	1.8	108	162	74	99	3.6	3.4
20.	1.0	2.5	6.7	7.6	3.6/3.1	5.8/1.8	0	0.6	0	0.5	3+	4+	1+	2+	7.4	2.1	190	282	130	169	1.6	2.3
21.	2.5	2.0	7.8	6.9	4.5/3.3	5.8/1.8	0.3	1.0	0.2	0.5	1+	3+	2+	2+	6.0	2.9	150	223	86	146	3.7	2.6
22.	8.0	1.5	5.7	7.3	3.0/2.7	5.2/2.1	0.3	1.1	0.3	0.6	1+	3+	0	2+	5.8	2.4	110	214	68	149	1.8	1.4
23.	2.5	2.0	6.7	6.9	4.9/1.8	4.7/2.2	0.1	0.8	0.1	0.6	4+	4+	2+	2+	5.8	3.1	102	290	89	185	2.0	3.0
24.	12.4	2.0	7.0	6.9	4.7/2.3	5.1/1.8	0.5	1.7	0.2	0.8	0	3+	0	2+	6.4	2.0	89	196	58	120	2.7	3.7
25.	5.0	2.0	6.9	8.0	3.9/3.0	5.0/3.0	0.1	0.7	0.1	0.5	3+	4+	2+	2+	6.7	2.5	115	219	85	127	2.1	1.9
26.	15.0	4.0	7.6	6.9	3.5/4.1	4.7/2.2	0.1	0.5	0.3	0.5	2+	3+	0	1+	8.2	4.0	130	215	80	144	4.7	4.6
27.	4.0	2.5	7.4	6.4	4.5/2.9	6.0/0.4	0.2	0.5	0.1	0.5	4+	4+	0	1+	5.3	1.6	122	208	83	133	3.0	1.6
28.	2.5	2.0	6.9	6.9	4.9/2.0	5.0/1.9	0.2	0.4	0.1	0.5	3+	4+	1+	2+	2.3	1.8	133	168	71	104	3.1	2.0
29.	7.0	4.0	9.1	6.4	4.9/4.2	5.0/1.4	0.4	1.1	0.4	0.4	0	3+	0	0	2.3	1.0	196	190	86	71	3.3	2.7
30.	4.5	0.0	6.7	6.5	3.8/2.9	4.6/1.9	0.2	0.9	0.1	0.7	1+	3+	0	0	2.6	2.3	132	221	84	138	2.5	1.9
31.	7.0	4.0	6.2	6.5	4.8/1.8	4.9/1.6	0.2	1.9	0.1	1.8	3+	4+	0	1+	3.0	2.1	137	192	85	120	1.5	2.6
32.	9.5	1.0	6.9	6.5	3.7/3.2	4.9/1.6	0.1	0.6	0.1	0.4	4+	4+	0	1+	6.4	2.0	82	208	53	141	1.9	2.5
33.	8.0	4.6	6.8	6.3	4.9/1.9	4.7/1.6	0.4	0.8	0.3	0.7	2+	4+	0	0	2.4	4.1	139	186	73	115	3.2	3.8
Total abnormal	27	3	2	1	19	4	13		3		32		12		24	7	19	6	12	3	5	1

* Total patients in series, 54; total patients examined by liver-function tests four weeks after completion of treatment, 33.
† B, results on admission; A, results four weeks after completion of treatment.

TABLE 3.—*Incidence of Liver Abnormality in Acute Malaria by Gross and Microscopic Examination* *

	Patients	
	No.	%
Liver abnormal	31	91.9
Gross	25	80.6
Microscopic	29	93.2
Gross and microscopic	23	67.7

* Total number of patients, 34.

Fig. 1 (Case 4).—Thirteen months in Korea. Symptoms started eight months after return. Grossly, the liver was moderately enlarged. Three mitotic figures involving liver cells. Hematoxylin and eosin; × 900.

chronic inflammatory cells, predominantly lymphocytes and mononuclear cells (Fig. 2). Hepatic architecture is deranged only with most severe involvement.

The microscopic sections were graded I, II, III, or IV, according to the degree of anatomic abnormality. The distribution of the cases in the four microscopic grades, evaluated before and after therapy, is shown in Table 4, 0 representing normal histology.

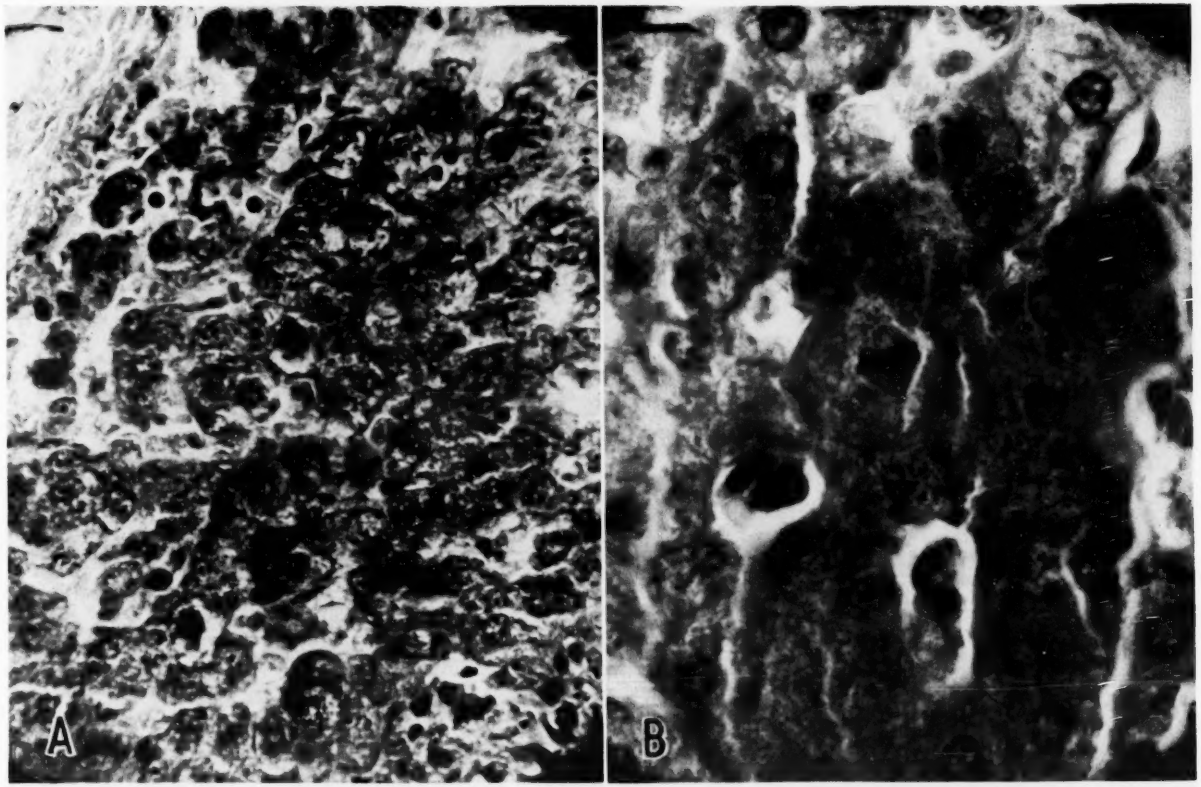

Fig. 2 (Case 29).—Eleven months in Korea. Symptoms started one month after return. The liver was enlarged moderately. *A*, smudging and clumping of liver cell cytoplasm, cellular infiltration of sinusoids, and numerous mitotic figures. Giemsa; × 475. *B*, mitotic figure and Kupffer cell hyperplasia. Hematoxylin and eosin; × 900.

An attempt was made to correlate the degree of microscopic abnormality with severity of liver dysfunction. No correlation was found (Fig. 3).

The liver was palpable in 22 (40.7%) of the 54 patients. Right upper quadrant tenderness was present in 10 additional patients (18.3%), in whom the liver was not enlarged. The spleen was palpable in 28 (51.8%).

TABLE 4.—*Grade of Pathologic Liver Changes in Acute Malaria, Evaluated Before and After Therapy*

Grade	Before Treatment		After Treatment	
	No.	%	No.	%
0	3	8.8	13	52.0
I	13	38.2	6	24.0
II	9	26.4	4	16.0
III	5	14.8	1	4.0
IV	4	11.8	1	4.0
Total	34	100.0	25	100.0

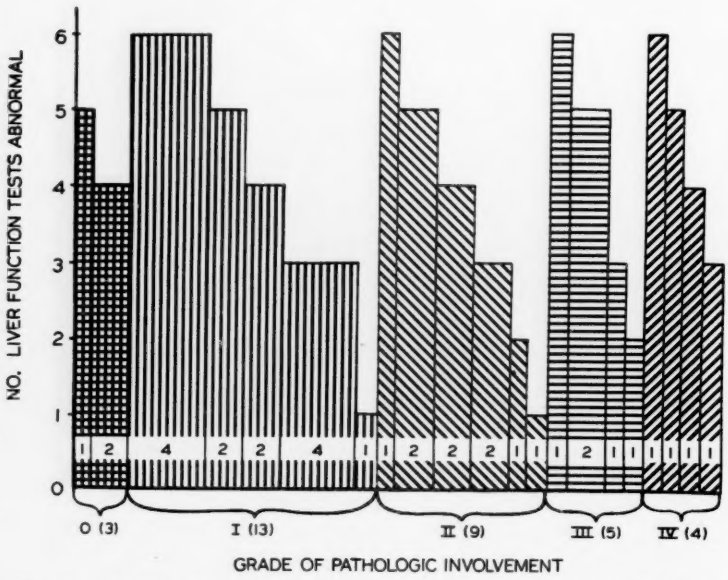

Fig. 3.—Incidence of abnormal liver-function tests in the four grades of pathologic involvement during acute malaria.

The most frequent hematologic abnormality was lymphocytosis. A relative lymphocytosis was present in 30 (55.5%) of the cases, and an actual lymphocytosis was present in 21 (50.7%). Fourteen patients had leucocytosis, and 14 had leucopenia. Anemia was present in 13 (24%) patients. All hemotologic studies reverted to normal during the period of hospitalization.

Serological abnormalities included positive Kahn precipitation tests in 27 (50%) patients, and 4 (14.8%) of these had positive Kolmer complement-fixation reac-

tions. All of the positive serological tests returned to normal by the time treatment was concluded. An elevated erythrocyte sedimentation rate occurred in 47 (90.3%) of the 52 cases so tested.

COMMENT

Hepatitis, although not always clinically evident, was present in all our patients. Liver sections obtained at postmortem examinations of fatal cases of malaria (usually falciparum malaria) fail to explain the mechanism by which malaria damages the liver. Fever, poor nutrition, anemia, anoxia, malaria toxin, and the presence of the parasite in hepatic tissue have all been offered as mechanisms by which the liver is damaged. No conclusive evidence has been presented to prove that any of these is the means by which the liver is affected. Patients with only one febrile episode have been evaluated and found to have definite liver damage. The nutritional status of each patient was excellent, thus eliminating this factor. A few instances of anemia were found, but there is no correlation in this series between anemia and liver damage. In no biopsy specimen was a malaria parasite identified, although many sections were stained by Giemsa's method. It is therefore impossible to offer any definite mechanism of liver damage from the findings of this study.

We have observed that changes in liver histology are temporary and begin to return to normal during the course of antimalarial therapy. As the average time from the cessation of suppressive therapy in the Far East to the date of admission was seven months, it is very improbable that the changes observed in biopsy specimens and in liver-function tests were due to these medications. In no case was there an increase in the degree of abnormality of the liver-function profiles or the amount of histological abnormality after treatment. In fact, all liver-function profiles improved with therapy, and improvement was observed in all but one follow-up peritoneoscopic biopsy.

SUMMARY AND CONCLUSIONS

Hepatitis was present in 52 cases of proved malaria in Korea veterans. The results of liver-function tests and peritoneoscopic liver biopsies are discussed.

Hepatitis is a feature of malaria rather than a complication.

The treatment of the hepatitis is as important as eradication of the parasitemia.

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TREATMENT OF SICKLE-CELL ANEMIA WITH COBALT CHLORIDE

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SICKLE-cell disease is a chronic familial abnormality of hemoglobin synthesis which is found almost exclusively in Negroes. The disease derives its name from the characteristic sickled appearance of the red blood cell after it is subjected to deoxygenation. There are two clinical states. Sickle-cell trait, in which there is no anemia, requires greater reduction in oxygen tension for sickling to appear than the second and clinically more significant type, sickle-cell anemia.[1] In the latter condition, there occur a hemolytic anemia, arthritis, leg ulcers, abdominal crises, gall stones, cardiomegaly, and changes in bodily configuration. The intravascular sickling which occurs is the major factor in the development of the hemolytic anemia. There are definite variations in the severity of the anemia produced. It is noteworthy that the patients being presented in this report were well enough to be inducted into the army.

Pauling, Itano, and others* used electrophoretic differences to find five distinct species of hemoglobins. Hemoglobin "a" is found in normal adults. Hemoglobin "f," or fetal hemoglobin, constitutes 55 to 98% of all the hemoglobin in infants. This form of hemoglobin is also found in hemolytic processes or chronic anemias and probably represents an attempt on the part of the marrow to form normal hemoglobin. The other three species are named "b," "c," and "d." Hemoglobin "b" is the type found most commonly in sickle-cell disease, but occasionally "c" or "d" hemoglobin is found together with "b." Persons with the trait alone have normal "a" hemoglobin plus "b." In sickle-cell anemia there is no "a" hemoglobin present in the erythrocyte, but there are varying amounts of hemoglobin "f" (2 to 25%) plus hemoglobin "b" alone or together with hemoglobin "c" or "d." The finding of these additional hemoglobins makes the problem of defining the genetic control of sickle-cell anemia more complex. The generally held hypothesis is that persons with the trait are heterozygous in the gene or genes which are responsible for the abnormal hemoglobins, while the anemic patients are homozygous.†

Although a great variety of therapeutic measures have been used in treating or trying to prevent hemolytic crises and in treating the existing anemia, none have met with great success. The very comprehensive review article by Margolies [17] lists the various therapeutic agents tried. We were influenced to try cobalt chloride in this disease because of the reported beneficial effect of cobalt on patients with Mediter-

From the Medical Service of the Veterans Administration Hospital.

* References 2-13.

† References 14-16.

ranean anemia.‡ In thalassemia, as in sickle cell anemia, there is a varying amount of fetal hemoglobin present. We were interested not in preventing crises but in attempting to raise hemoglobin levels. It has been thought that patients with sickle-cell anemia have adjusted themselves to their chronic anemia and require no treatment for it. However, we have been so impressed by the increased sense of well-being that has occurred in the few patients that have been transfused that we thought it worth while to attempt to correct the long-existing anemia in the patients to be reported. The increased efficiency and sense of well-being that occurred in each of the patients have confirmed this impression.

Cobalt has been found of value in the treatment of other anemais beside thalassemia. It has been used in the treatment of anemias secondary to chronic infection, carcinoma, uremia, leukemia, and lymphoma.§ In many of the cases, iron alone was not as effective. While cobalt has been long known to produce polycythemia in many different laboratory animals,|| its mode of action is not clear. In rats cobalt will not produce polycythemia if iron deficiency exists ¶; consequently, it may be that cobalt exerts its stimulating effect through increasing the utilization of iron.# In cattle a true cobalt deficiency exists and will produce anemia *; in humans there is no evidence that such a deficiency occurs. Since most cobalt-treated patients and animals show an increase in serum bilirubin, it has been suggested that the primary action of cobalt is to cause increased hemolysis, with resultant compensatory hematopoiesis.[44] It would seem, however, that the signs of increased hemolysis are due to the production of immature and more fragile cells following intense erythropoietic stimulation rather than to a primary toxic effect of cobalt. Since local bone marrow anoxia is the stimulus par excellence for red cell formation,[45] the possibility of cobalt producing local bone marrow anoxia has been investigated. It is known that cobalt produces vasodilatation of capillaries.[46] If such a dilatation occurred in the bone marrow, the resultant stasis would produce anoxia. The other possibility, and this seems more likely, is that cobalt poisons the essential respiratory enzymes controlling the oxidative and reductive processes in the marrow, with resultant anoxia.† Such agents as liver extract and sulfhydryl group donors have been shown to nullify and counteract the effects of cobalt.‡ No matter what its mechanism of action, cobalt has profound stimulating effect on erythropoiesis § and, to some extent, on granulopoiesis.[19] This is evidenced by a prompt reticulocytosis with subsequent rise in red blood cells and hemoglobin. The peripheral smear shows all forms of immature red cells, but other than that the cells formed under the stimulus of the cobalt do not differ from normal red blood cells.||

‡ References 18 and 19.
§ References 20-27.
|| References 27-38.
¶ References 38 and 40.
# References 19 and 41.
* References 42 and 43.
† References 19, 23, 34, and 47-49.
‡ References 50-52.
§ References 53 and 54.
|| References 55-57.

METHOD

The four patients used in this study have been followed for several years, either at this hospital or at the New York Regional Office of the Veterans Administration. We thus had a long baseline control period, during which many forms of therapy had been used unsuccessfully. At the time of the patients' admission to the hospital complete physical and laboratory examinations were performed. After a suitable control period, the patients were given 12 cc. of a 2.5% aqueous solution of cobalt chloride divided into three doses.[20] The solution was given in a glass of orange juice immediately after meals. Red blood cell count, hemoglobin determination, reticulocyte counts, and serum bilirubin determinations were done regularly. After four weeks of therapy 1.8 gm. of ferrous sulfate was given daily together with the cobalt[19] for two additional weeks. Then all medication was stopped and the patients were observed for a period of at least two weeks before discharge, except for the fourth patient, for whom we plan to continue cobalt therapy indefinitely.

RESULTS

In all four of the patients with sickle-cell disease there was a definite symptomatic response. In three cases the improvement was dramatic. The improvement symptomatically in the third case was only slight, but the patient attained normal hemoglobin and red cell values. The peak effect on the red cell count occurred in the third week of therapy, while the maximum reticulocytosis occurred during the first week. There was a secondary peak in the reticulocytosis three weeks after the start of cobalt therapy in the first case and 14 days after the start of therapy in the second case. Such secondary peaks have been described in animals.[19] The blood smears were all characterized by polychromasia and a great number of stippled cells, Howell-Jolly bodies, and normoblasts. These were not seen prior to treatment. There was no change in the percentage of sickling.

The first patient showed a fall in his serum bilirubin while on therapy. The second case exhibited the expected rise, whereas there was no appreciable change in the third and fourth cases. The decrease in bilirubin seen in the first patient is of great interest. The patient for many years had had a serum bilirubin level that ranged from 3 to 5 mg. per 100 cc. It seems unlikely that there was any decrease in the usual breakdown of his red cells, and there was the expected appearance of presumably more fragile immature cells. One possible explanation is that with the decrease in anoxia the liver was better able to handle the bile pigment.

The addition of iron was of no benefit in the three cases in which it was used, except that there was a slight increase in the red cell count in the third case. It is conceivable that if an iron deficiency had existed some further improvement might have been obtained. In the brief follow-up periods a fall in the red cell count and hemoglobin level was seen, although the patients still felt better than they had on admission.

REPORT OF CASES

CASE 1.—A 29-year-old Negro man first knew of his disease in 1944, while in the Army, when he was hospitalized for jaundice and anemia. There was only one previous episode of jaundice at the age of 5 years. Since 1944 he has had five hospital admissions. One was to the surgical service because of acute abdominal pain, which was finally thought to be due to sickle-cell crisis. During each of these admissions he was found to be severely anemic and icteric.

His average hemoglobin level was below 8.0 gm., and the red cell count was below 2,500,000 (Chart 1). On one occasion, after 3,500 cc. of blood was administered, the red blood cell count rose to 4,300,000 and the hemoglobin increased 14.5 gm.

The patient was admitted in February, 1953, because of abdominal pain, weakness, and dyspnea on exertion. Examination disclosed an underdeveloped Negro man, 5 ft. 4 in. (163 cm.) in

height, weighing 98 lb. (44.1 kg.). The sclerae were icteric; the mucous membranes were pale. The head was large for the general bodily configuration, with very small ears. He had arachnodactylia. There was early clubbing of the fingernails. There were systolic murmurs at the apex and base of the heart, which was not enlarged. The liver and spleen were not felt. There was a healed ulcer over the right knee.

The significant laboratory work is shown in Table 1. Results of the remainder of the hematologic and chemical studies were normal. The x-ray of the chest showed no abnormalities;

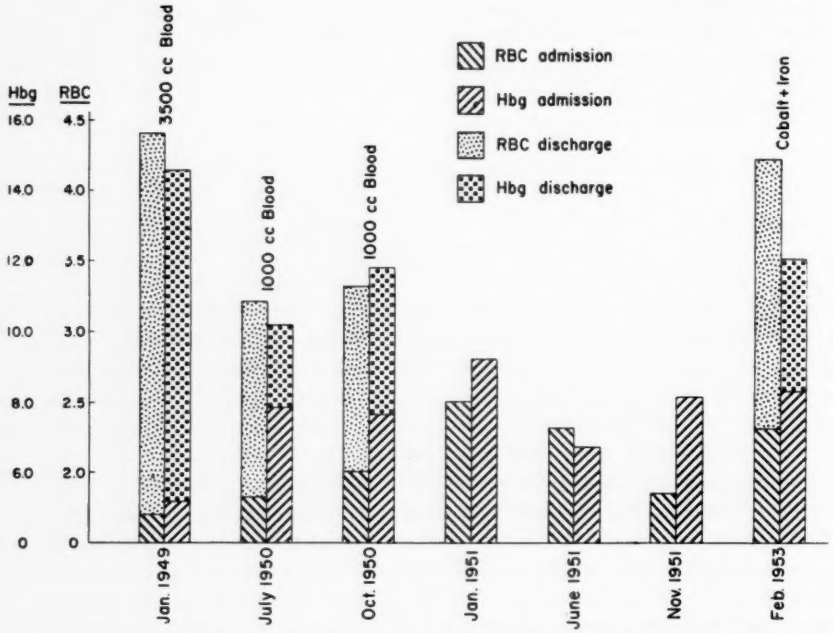

Chart 1 (Case 1).—Hemoglobin and red blood cell values since 1949. In 1951 the patient was not admitted to the hospital and the counts were done during outpatient visits.

TABLE 1.—*Laboratory Studies in Case 1*

	Admission	After 6 Wk. of Treatment	After Treatment
RBC, million	2.3	4.2	3.1
Hb, gm.	8.7	12.0	10.1
Reticulocytes, highest % attained	3.7	20.0	2.0
Sickling, %	90-100	90-100	90-100
Serum bilirubin, mg./100 cc.	3.8	1.0	2.9

the gall bladder series showed calculi. There were numerous areas of translucent densities scattered throughout the skull, mostly in the parietal region, and small conglomerate punctate lucent areas in the diploic region of the skull. There was osteoporosis of the vertebral bodies.

The patient was observed for two weeks and then was given 300 mg. of cobalt chloride, as outlined above. After four weeks of therapy, 1.8 gm. of ferrous sulfate daily was given in combination with cobalt for an additional two weeks. The abdominal pain had disappeared before the treatment was started, but the weakness had persisted. After the first week of therapy the patient felt stronger, regained his appetite, and became much less short of breath. The reticulocytes promptly increased to 20%, with a concomitant rise in red cell count and hemo-

globin level (Chart 2). There was no change when iron was added. Two weeks after the cessation of all medication, the hemoglobin fell to 10.1 gm. and the red cell count to 3,100,000. However, the patient continued to feel well.

CASE 2.—A 29-year-old Negro man first knew of his sickle-cell disease in 1943. However, when he was a child he was seen by a physician for "heart trouble." Since 1943 he has been hospitalized at various institutions 23 times, for anemia, jaundice, abdominal pains, palpitation, polyarthritis, or leg ulcers. During this period of observation, even after transfusions, his highest blood value was 12.4 gm. of hemoglobin with 3,900,000 red cells. His average hemoglobin during this period was 9.0 gm., and the red blood cell count averaged 3,000,000. He was admitted for the 17th time to the Bronx Veterans Hospital, because of weakness and abdominal pain, in April, 1953.

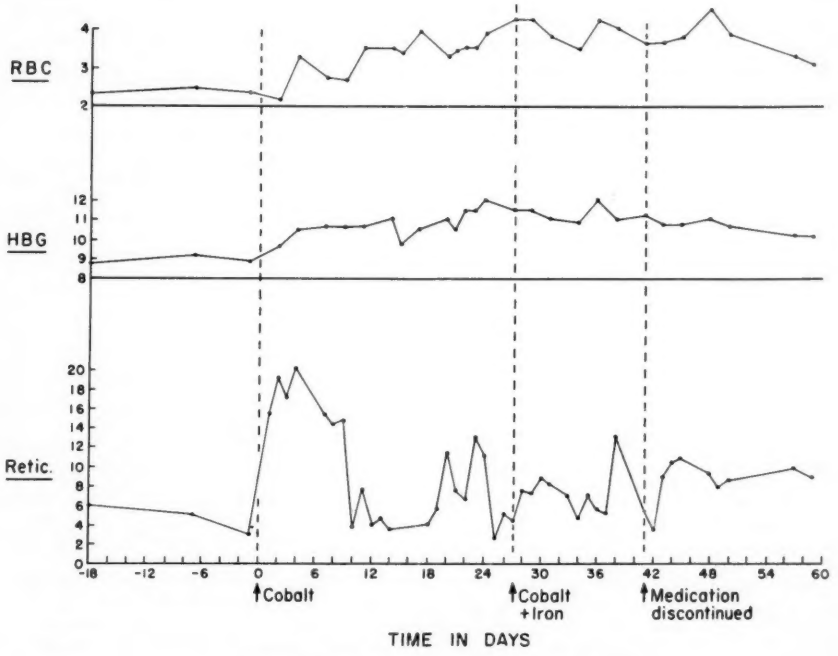

Chart 2 (Case 1).—Response to cobalt therapy.

He appeared well developed. He had a "tower head" and spider fingers. There was no icterus. He had a Grade 2 apical systolic murmur. The liver was slightly enlarged, and the spleen was not felt. There were well-healed scars over both internal malleoli. There was a generalized shotty adenopathy.

The significant laboratory work is included in Table 2. Results of all blood chemistry studies were normal, and the x-rays showed typical findings of sickle-cell anemia, with cortical thickening of the long bones and fish-tail appearance of the thoracic vertebrae.

After three days of observation, the patient was given 300 mg. of cobalt chloride daily for four weeks, and then 1.8 gm. of iron were added for another two weeks. The patient's symptomatic response was striking and was even more dramatic than the hematologic one. He felt better than any time in the past, including periods after multiple transfusions. The pain disappeared; he had a sense of well-being and lost his sense of easy fatigability. The addition of iron did not further improve the blood picture nor the symptomatic response. A month after cessation of treatment, the patient still felt well, although there was some fall in the red cell count and hemoglobin level (Table 2).

CASE 3.—A 49-year-old Negro man has been under observation since 1945 for sickle-cell anemia. His principal complaints have been weakness, easy fatigability, and vague aches and pains. On occasions he had been told that his sclerae were yellow. Unlike the other patients, he was able to function well enough so that it was not necessary to hospitalize him, until March, 1953, when he was admitted to the Bronx Veterans Hospital for the first time. During the period of observation his highest recorded red cell count was 3,900,000, and he had at that time 11.5 gm. of hemoglobin.

On admission he was not icteric and he displayed none of the usual physical stigmata of sickle-cell anemia. The significant laboratory studies are recorded in Table 3. Urinalysis gave evidence of a urinary tract infection, with numerous white cells in the sediment. X-rays of the bones displayed the expected bone changes seen in sickle-cell disease.

After a three-week observation period the patient was given the outlined course of cobalt therapy. The peak reticulocyte response, which was only 9%, was reached in seven days. After four weeks of cobalt therapy he had 15.5 gm. of hemoglobin, with 4,950,000 red cells. After iron therapy was added, his red cell count rose to 5,300,000. Toward the end of the fifth week of

TABLE 2.—*Laboratory Studies in Case 2*

	Admission	After 6 Wk. of Treatment	After Treatment
RBC, million	3.63	4.80	4.3
Hb, gm.	9.3	12.0	10.6
Reticulocytes, highest % attained	7.0	12.5	8.0
Sickling, %	95	95	95
Serum bilirubin, mg./100 cc.	0.8	1.5	1.0

TABLE 3.—*Laboratory Studies in Case 3*

	Admission	After 6 Wk. of Treatment	After Treatment
RBC, million	3.9	5.3	4.3
Hb, gm.	11.2	15.5	12.8
Reticulocytes, highest % attained	1.0	9.0	2.4
Sickling, %	95	95	95
Serum bilirubin, mg./100 cc.	1.1	1.2	0.9

therapy thrombophlebitis of the right saphenous vein developed. The medication was discontinued, and within a week the red cell count fell to 4,080,000, with 13.4 gm. of hemoglobin. After the phlebitis had subsided, the patient was again given cobalt and his red cell count rose to 5,000,000, with 14.7 gm. of hemoglobin, at which time there was a recurrence of a bilateral thrombophlebitis, which necessitated the discontinuance of therapy. Perhaps because he was not as anemic to begin with as the other patients, this patient's symptomatic response was slight. There was also some anorexia and nausea with the administration of cobalt.

This patient had persistent urinary tract infection, probably a bilateral pyelonephritis, which had proved resistant to antibiotic therapy. There is a possibility that some of his anemia was due to chronic infection rather than sickling and that the cobalt exerted its effect on such an anemia. It would be difficult to separate the two causes for anemia in this patient. However, in 1947 he had the same degree of anemia as he had on admission and at that time he had no urinary tract infection.

CASE 4.—This patient, a 24-year-old Negro man, first knew of his sickle-cell disease in 1947, when he was admitted in abdominal crisis to an army hospital. Since then he has been admitted to this hospital on three occasions, complaining of joint and chest pains and weakness. During this six-year period, his hemoglobin never exceeded 11.0 gm. per 100 cc. and his red blood count did not exceed 3,500,000 per cubic millimeter.

He was admitted for the fourth time, on July 12, 1953, complaining of migratory arthritis and weakness of three weeks' duration. One week after the onset of his symptoms he was seen at another hospital, where he was given a 1,000 cc. blood transfusion without benefit.

He appeared small, wiry, and poorly nourished. The heart was markedly enlarged, and there was a Grade II apical systolic murmur. The spleen was not felt. The remainder of the examination was noncontributory. The significant laboratory work is included in Table 4, and results of the other laboratory examinations were normal.

His joint complaints subsided prior to his being given cobalt chloride, which was started a week after admission. There was some mild transient epigastric burning after the first few doses of cobalt. Within a week he began to feel stronger and better than he had felt in a long time. There was a 2 gm. rise in hemoglobin during this one-week period. At the end of six weeks there was a significant improvement in the hemoglobin level and red cell count (Table 4). The highest reticulocyte count was 10%. At the time of discharge the heart was smaller and the systolic murmur was no longer audible. It is planned to have this patient continue taking cobalt for a protracted period of time.

TOXICITY

In doses of 300 mg. of cobalt per day there is frequently nausea, vomiting, anorexia, or diarrhea.¶ One case of temporary nerve deafness has been reported to have occurred with this drug.[27] Fortunately the deafness disappeared after the medication was discontinued. In animals there have been reports of renal injuries. Cobalt is excreted in the urine and may produce its damage when in high concentration in the urine.#

TABLE 4.—*Laboratory Studies in Case 4*

	Admission	After 6 Wk. of Treatment
RBC, million	3.36	4.11
Hb, gm.	9.3	13.6
Reticulocytes, highest % attained	0.9	10
Serum bilirubin, mg./100 cc.	1.8	1.2

Gastrointestinal irritation was seen in the last two cases. This was mild and temporary and did not interfere with the treatment. One patient had two separate episodes of thrombophlebitis, each occurring two weeks after the start of cobalt therapy (he was given two separate courses). This complication has been seen in sickle-cell disease but has not been reported as a complication of cobalt therapy. We have treated 11 patients with cobalt chloride. Seven patients had diseases other than sickle-cell anemia. Five patients had symptoms of gastrointestinal irritation. One patient developed erythema multiforme in addition, and another had a generalized urticarial reaction. Both skin eruptions faded after cobalt therapy was stopped. These seven patients plus the four patients with sickle-cell disease who have been described in detail above were all given 300 mg. of cobalt daily.

CONCLUSIONS

Cobalt therapy offers promise of being an effective means of improving the chronic anemia of patients with sickle-cell disease. Its degree of effectiveness may conceivably depend on the percentage of fetal hemoglobin present in the red blood cells. In those cases with a higher percentage of such hemoglobin, the bone marrow may be better able to respond to the stimulation of cobalt. The high incidence of toxicity in our small series of cases is due to the relatively high dosage. The proper dosage of cobalt must depend on much wider experience. The choice of a six-week

¶ References 19, 20, 23, and 27.

References 58 and 59.

period of study was arbitrary, and it might well be that prolonged administration of cobalt might have increased the red cell count and hemoglobin to higher levels. This is being attempted in the fourth case. It is hoped that this preliminary report will stimulate others, with greater amounts of clinical material at hand, to use cobalt therapy for their patients with sickle-cell disease.

SUMMARY

Four patients with sickle-cell anemia were treated with 300 mg. of cobalt chloride daily for six weeks. They received 1.8 gm. of iron daily for the last two weeks of this period.

In all four patients there was both symptomatic and hematologic improvement.

The mode of action and toxicity of cobalt are discussed.

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CLINICAL EVALUATION OF ERYTHROMYCIN

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ERYTHROMYCIN is the generic name of an antibiotic derived from Streptomyces erythreus. Its discovery, method of production, and isolation as a crystalline material were described in June, 1952, by McGuire and co-workers.[1]

Erythromycin is a basic compound soluble to the extent of 2 mg. per milliliter in water. It is extremely soluble in organic solvents, such as alcohol, acetone, chloroform, and ethyl acetate.[1] The crystalline material is grayish white and is stable at room temperature. The pH of a saturated solution of erythromycin is approximately 9. Aqueous solutions in high and low concentrations are stable for eight weeks at 4 C. in a frozen state. At room temperature there is some deterioration during the first week, but none has been demonstrated in the ensuing seven weeks. The antibacterial activity of broth solutions begins to decline on the fourth day. After this there is continuous progressive deterioration. Heating the material from 60 to 100 C. for 15 minutes causes significant loss of activity.* Dilute solutions may be filtered through Berkefeld filters with only slight loss of activity.†

An acid pH is very destructive to erythromycin. At a pH of less than 4 there is little or no demonstrable antibacterial action.‡ Its activity is increased with increasing alkalinity of the medium; this increase is roughly tenfold for each pH unit.[4] Serum, sodium chloride, dextrose, paraaminobenzoic acid, and reduced oxygen tension have been reported not to affect the activity of erythromycin.

Several investigators § have reported a low degree of toxicity of erythromycin in man and animal. The L. $D._{50}$ in mice by the subcutaneous route is 1,800 mg. per kilogram.[1] Chronic toxicity studies in mice and dogs have demonstrated an extremely low degree of toxicity of the antibiotic.

Haight and Finland [2] have reported that the in vitro spectrum of erythromycin is wider than penicillin but not as wide as chlortetracycline, chloramphenicol, or oxytetracycline. On a weight basis erythromycin is more active against the Gram-

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The erythromycin used in this study was supplied by Dr. J. W. Smith, of the Eli Lilly & Company Research Laboratories, and Dr. L. E. Josselyn, of the Abbott Laboratories.

* References 2 and 7.

† References 2 and 7.

‡ References 2 and 7.

§ References 1, 2, and 4.

positive but less effective against the Gram-negative organisms than is oxytetracycline, chloramphenicol, or chlortetracycline. Erythromycin is about equally effective against Hemophilus.

In vitro studies by Haight and Finland [2] and by Heilman and co-workers [4] revealed that all streptococci were inhibited by concentrations of 3.1 γ per milliliter. Groups A, B, and C were more sensitive than Group D. All the strains of micrococci tested were inhibited by concentrations of 3 γ per milliliter or less. Neisseria, Hemophilus, and the clostridial organism were also quite sensitive, as well as some strains of Brucella. None of the Gram-negative bacilli were sensitive.

Erythromycin has been shown to exert its effect only against actively multiplying bacteria. It is bactericidal against the most sensitive organisms, and to less sensitive species it is bacteriostatic only, unless higher concentrations are used.[6]

Naturally occurring variants of erythromycin-sensitive strains of bacteria have not yet been demonstrated. However, when erythromycin-sensitive bacteria are exposed to gradually increasing concentrations of the antibiotic, strains of increased resistance are obtainable.[9] The rate at which the adaptation to growth in higher concentrations develops varies with the strain of bacteria. Hemolytic streptococci develop resistance less rapidly than do staphylococci, enterococci, or pneumococci.[9] The natural resistance of certain organisms to erythromycin apparently does not depend on their ability to produce "erythromycinase," as none has been demonstrated.[6]

The absorption of erythromycin takes place in the upper gastrointestinal tract or from the rectum, where it is readily but irregularly absorbed. Higher blood levels are obtained if the drug is given before rather than after meals.[3] Gastric juices are destructive to this antibiotic, and for this reason coated tablets have been prepared to protect it from this destructive effect. This coating also masks the bitter taste of the drug. Josselyn and Sylvester,[3] as well as Heilman and co-workers,[4] have studied the effects of administering alkali along with the erythromycin. The former group has reported that aluminum hydroxide exerts some protective effect against the deteriorating effect of the gastric juice.

Serum levels following the oral administration of 500 mg. of the drug in coated tablets are in the range of 1 to 2 γ per milliliter at two, four, and often at six hours. These levels are above the in vitro sensitivity of most susceptible organisms. In order to maintain satisfactory blood levels in adults it appears to be necessary to administer 400 to 500 mg. of erythromycin every six hours.

Erythromycin apparently does not readily diffuse into the spinal fluid in normal people. There is placental transmission and some evidence of diffusion into ascitic and pleural fluids. It is excreted by the liver and concentrated in the bile. Large amounts appear to be constantly excreted in the urine, and it is also found in varying amounts in the stool.[4]

Animal protection studies have shown that mice fed erythromycin remained well when several times the lethal dose of Pneumococcus was given intraperitoneally. Similar studies have shown that erythromycin protected mice against 1,000 lethal doses of the psittacosis virus.[4]

Eight of nine guinea pigs inoculated subcutaneously with 10 lethal doses of Corynebacterium diphtheriae survived after 2 mg. per kilogram per day of erythromycin was given intraperitoneally. Nine untreated controls died within four days.[4]

Mice infected intracerebrally and intranasally with Hemophilus pertussis appeared to be protected as well by erythromycin as by chlortetracycline, chloramphenicol, or oxytetracycline. Endamoeba histolytica is very sensitive to erythromycin in vitro, and rats infected with amebae have been cured with the antibiotic.

Clinical reports to date || indicate that erythromycin is an effective antibiotic in the treatment of pneumococcal pneumonia, streptococcal pneumonia, streptococcal pharyngitis, pertussis, gonorrhea, diphtheria carriers, and some staphylococcal septicemias. In the treatment of endocarditis it has been less impressive, with failures being reported. Micrococcus enteritis as a complication of antibiotic therapy has been successfully treated with erythromycin.[10]

The present clinical study of erythromycin began at Jefferson Davis Hospital in July, 1952. Patients were selected on the basis of a known or suspected bacteriological diagnosis. Many were treated only after in vitro sensitivity studies demonstrated that the causative organism was sensitive to erythromycin or that it was resistant to other antibiotics. A large percentage of the patients were severely ill with overwhelming infection. All of the patients except two were adults.

The diseases treated included pneumococcal pneumonia, streptococcal pharyngitis, streptococcal and staphylococcal septicemias, subacute and acute bacterial endocarditis, acute gonorrheal urethritis and cervicitis, wound infections, lung abscesses, and empyema. Two patients with Bacterioides infections were also treated. The dose of erythromycin used was 25 mg. per kilogram per 24 hours in all but one case. This patient received 10 mg. per kilogram. In the beginning of the study, erythromycin was given in capsule form with meals or with milk. Later, coated tablets were given before meals. Two patients received erythromycin intravenously. The duration of treatment ranged from 3 days to 100 days. Routinely, erythromycin was administered for 72 hours after the patient was afebrile and clinically well.

Bacteriological studies were done in the general bacteriology laboratory and in the Ben Taub Infectious Disease Laboratory. In every instance a specific diagnosis of the etiological agent was made. In vitro sensitivity tests were performed, using the disc method in all cases. In those patients with blood stream infections, the tube-dilution technique was also used. In these cases it was further determined whether or not erythromycin was bacteriostatic or bactericidal in its action against the particular organism. Erythromycin blood serum levels were not determined.

RESULTS

A summary of the clinical results obtained in 29 patients treated with erythromycin is presented in the Table.

Pneumococcal Infections.—The results in the treatment of eight patients with pneumococcal pneumonia, three of whom had bacteremia, were good. The only failure was that of a Negro man treated with 200 mg. of erythromycin in capsules every six hours, which probably represented an inadequate dose. Case 1 is an example of the good response of pneumococcal pneumonia to erythromycin.

CASE 1.—A 65-year-old woman was admitted to the hospital on the fourth day of her illness. She complained of a cough of four days' duration, productive of ½ oz. (14 gm.) of brown sputum daily. Three days before admission a chill had occurred, and this was followed by fever, left pleuritic chest pain, and moderate dyspnea.

|| References 5 and 8.

Physical examination revealed an acutely ill white woman with labored breathing and temperature of 103 F. The findings of infiltration and beginning consolidation were present at the left lung base anteriorly.

An x-ray film made of the chest demonstrated this area of increased density in the left lung. Pneumococci were isolated from the admission blood and sputum cultures. The white blood cell count was 15,360, with 87% polymorphonuclear leucocytes.

Four hundred milligrams of erythromycin was given every four hours for eight days. The prompt response is illustrated in Figure 1.

The seven other patients with pneumococcal pneumonia responded equally well. No patient was febrile after 48 hours of therapy. Sputum cultures were negative after 48 hours, and none of the patients developed any complication of pneumonia. The longest period of administration of erythromycin in this group was nine days.

Streptococcal Disease.—Five patients with streptococcal pharyngitis responded favorably to erythromycin. The febrile response and the time required for local

Infections Treated with Erythromycin

Causative Organism	Disease	Cases, No.	Results			Comment
			Good	Doubtful	Failure	
Pneumococcus	Pneumonia	8	7	0	1	Failure, treated with 200 mg. capsules every 6 hr.
Hemolytic streptococcus	Pharyngitis	5	5	0	0	
	Septicemia	2	2	0	0	
Nonhemolytic streptococcus	Subacute bacterial endocarditis	1	0	0	1	
Staphylococcus (Micrococcus)	Acute endocarditis	1	0	0	1	
	Subacute endocarditis	1	0	0	1	Good clinical response, but relapse
	Acute suppurative bronchitis	2	2	0	0	
	Septicemia	4	4	0	0	Two treated with erythromycin, I.V.
	Empyema	2	1	1	0	Good febrile response, empyema cavity not sterilized
	Infected fracture	1	1	0	0	
Bacterioides	Empyema	1	1	0	0	
	Septicemia	1	0	1	0	

symptoms and signs to disappear were comparable to those seen with penicillin therapy.

Two patients with beta hemolytic streptococcus septicemia were treated, and both responded promptly. In one instance the septicemia was secondary to a furuncle on the right breast. The second is summarized as follows:

Case 2.—A 21-year-old white woman developed chills and fever 36 hours after extraction of an abscessed tooth. Blood cultures and cultures taken from the alveolar socket revealed a beta-hemolytic Streptococcus. Figure 2 illustrates the prompt response to erythromycin.

Blood cultures taken 48 hours after erythromycin therapy were negative for pathogens in both these cases.

One patient with subacute bacterial endocarditis was treated with erythromycin alone.

Case 3.—A 30-year-old white woman was admitted to the hospital with a five-month history of progressive heart failure, fever, pallor, hemoptysis, and weight loss. Six months prior to admission a careful examination had revealed no heart murmurs. For three years the patient had been taking diacetylmorphine (heroin) intravenously, using an unsterile syringe and needle.

Examination revealed petechial hemorrhages in both conjunctivae, mucosal and skin pallor, dyspnea, orthopnea, and dependent edema. There was evidence of cardiac enlargement, and there were both aortic and mitral systolic murmurs and an aortic diastolic murmur. The pulse was of celer contour.

The liver and spleen were enlarged and tender. There were multiple septic infarcts on the fingers and toes.

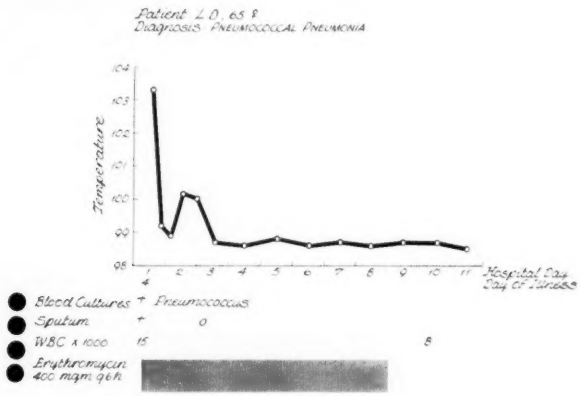

Fig. 1.—Prompt response of pneumococcal pneumonia to erythromycin.

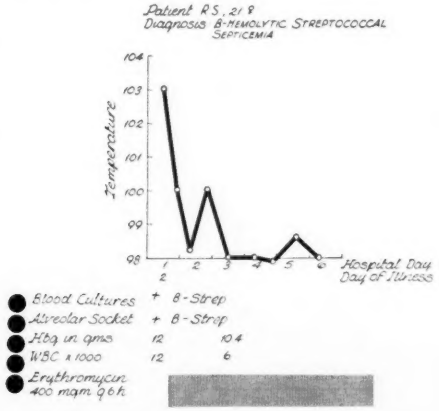

Fig. 2.—Prompt control of a hemolytic streptococcal septicemia.

Beta hemolytic streptococci, identified as Streptococcus faecalis, were isolated from the blood. Tube-dilution sensitivity studies demonstrated that the growth of this organism was inhibited by 0.2 γ of erythromycin per milliliter. However, erythromycin was shown to be bacteriostatic only in its effect against this organism in concentration up to 15 γ per milliliter.

Five hundred milligrams of erythromycin was administered every six hours from the third to the eighth hospital day. Blood cultures continued to be positive for Str. faecalis; a low-grade fever persisted, and the patient's general condition deteriorated.

Erythromycin was stopped and oxytetracycline, streptomycin, and penicillin were started in the dosage indicated in Figure 3. However, blood cultures continued to be intermittently positive, and septic emboli to the lungs and extremities continued to occur. Congestive heart failure was responsible for the patient's death, on the 22d hospital day.

This case undoubtedly represents a treatment failure. However, certain facts concerning the case are worthy of note. First, with respect to the nature of the illness, it is well known that subacute bacterial endocarditis is difficult to cure with a bacteriostatic agent. Second, the patient received capsules of erythromycin, and

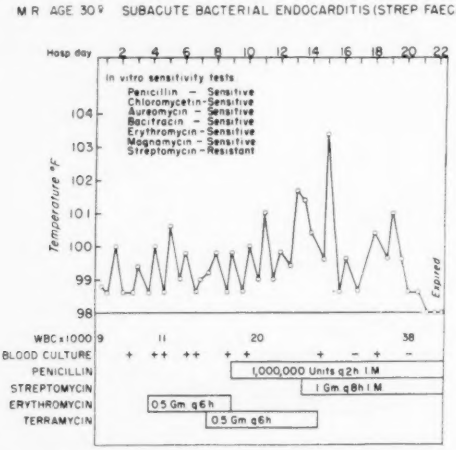

Fig. 3.—Failure of erythromycin treatment of enterococcal endocarditis.

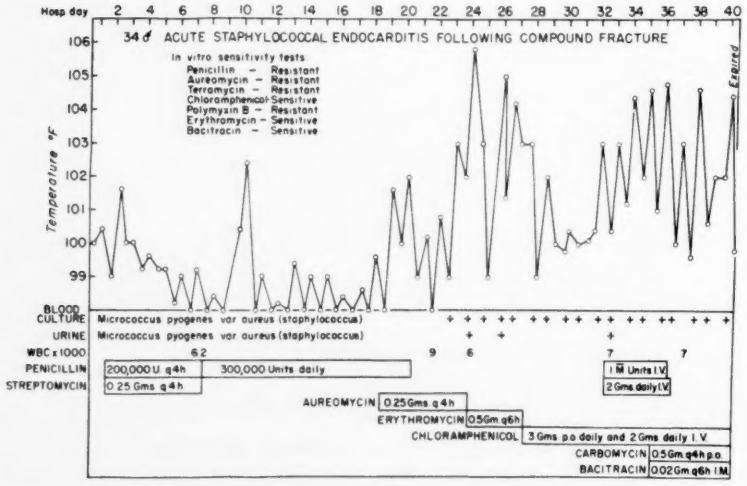

Fig. 4.—Failure of erythromycin in acute staphylococcal endocarditis.

effective blood levels may not have been obtained. Severe heart failure was present on admission. This, along with the duration of the patient's illness (at least five months) and the aortic involvement, has been shown to be of grave prognostic significance.

Nine patients with streptococcal endocarditis have subsequently been treated successfully with a combination of streptomycin and erythromycin.

Staphylococcal (Micrococcic) Infections.—Eleven patients, all with severe staphylococcal infections, were treated with erythromycin. Ten patients recovered and one died. Two patients with acute suppurative bronchitis, resistant to other antibiotics, improved after erythromycin therapy. Four patients with staphylococcal septicemia were treated (two with intravenous erythromycin), and all of them recovered. Staphylococcal empyema was treated in two cases, and in both there was a suppression of the systemic symptoms. However, the empyema cavity was not sterilized. One patient with an overwhelming staphylococcal infection complicating a compound fracture of the tibia was not cured of the infection with erythromycin. The organism was resistant to penicillin. The following is a summary of this case:

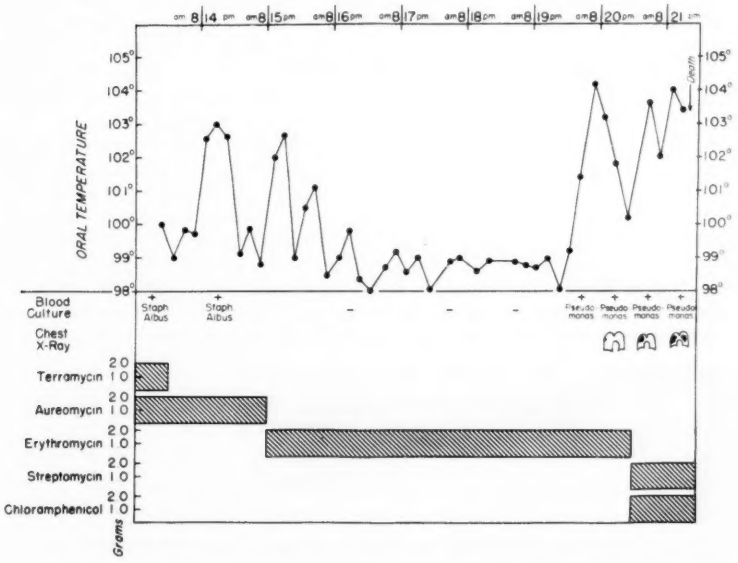

Fig. 5.—Effectiveness of erythromycin in controlling a staphylococcal bacteremia.

CASE 4.—A 34-year-old white man was admitted to the hospital because of a compound fracture of the right tibia. He had been previously well. The fracture was treated by wound débridement and by reduction and internal fixation of the fragments.

The immediate postoperative course was uneventful except for a low-grade fever during the first three days. Chills and fever began on the 19th postoperative day and continued throughout the remainder of the hospital course.

Figure 6 illustrates the lack of response to the antibiotics administered and summarizes the pertinent laboratory data. It is to be noted that on the 23d hospital day and daily thereafter a hemolytic Staphylococcus aureus (Micrococcus pyogenes var. aureus) was isolated from the blood stream. In vitro sensitivity studies demonstrated that the growth of the organism was inhibited by 0.1 γ of erythromycin per milliliter.

On the 24th hospital day erythromycin (0.5 gm. every six hours) was begun and was administered for four days. There was no response to this medication. Peripheral arterial emboli to the extremities and the brain occurred. Splenomegaly was noted, with marked tenderness in the right upper quadrant, and blood cultures remained positive.

Other antibiotics were then begun, as illustrated in Figure 6. On the 38th hospital day the abdomen was explored for an splenic abscess, but none was found. The same day a Grade 3 aortic diastolic murmur became audible. On the 40th hospital day the patient died.

In this case erythromycin failed to effect a clinical or a bacteriological response. Blood cultures continued to demonstrate just as many colonies of Staphylococcus during therapy as before. A relatively low white cell count was consistently present and indicated the lack of a defense to the infection. The lack of response to any of the antibiotics given demonstrates again the seriousness of acute staphylococcal endocarditis.

The following is a summary of a case in which the staphylococcal infection was controlled by erythromycin, but the patient subsequently died of a Pseudomonas infection that developed during therapy:

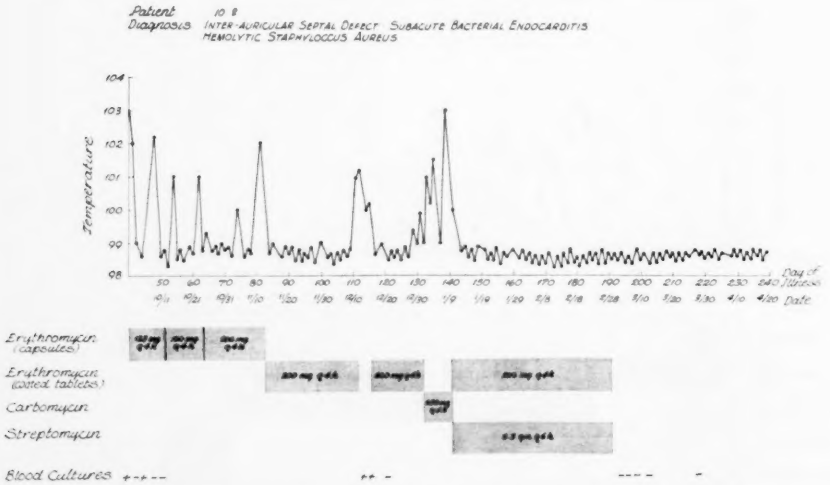

Fig. 6.—Failure of erythromycin alone to control a staphylococcal endocarditis and the success of the combination of streptomycin and erythromycin.

CASE 5.—A 43-year-old farmer was first admitted to the hospital on July 30, 1951, complaining of weakness and dizziness. He was found to have a severe anemia, and the diagnosis of myelofibrosis with myeloid metaplasia was ultimately established. From the time of the first admission to the last admission, on Aug. 14, 1952, it was necessary to admit the patient to the hospital 16 times for blood replacement and the treatment of frequent respiratory tract infections. During this time the number of polymorphonuclear leucocytes decreased to less than 5% of the total leucocytes. The infections required treatment with penicillin, chlortetracycline, oxytetracycline, and chloramphenicol.

After a blood transfusion during the next to the last admission, chills and fever developed. The chills subsided, but the patient continued to run a low grade fever, notwithstanding oxytetracycline therapy. Repeated blood cultures were all positive for Staphylococcus albus (M. pyogens var. albus). This organism was found to be resistant in vitro to all the usual antibiotics but was sensitive to erythromycin. The patient was consequently readmitted to the hospital and given 2 gm. of erythromycin daily, with a prompt drop in temperature and general improvement. On the fifth day of erythromycin therapy, however, a shaking chill, high fever, and acute right chest pain developed. A few hours later roentgenological examination of the chest revealed an area of

density in the upper lobe of the right lung laterally. The following day the chills and fever persisted and the pulmonary disease progressed very rapidly. The sputum contained streaks of blood and was very tenacious. It was the clinical impression that the patient had a superimposed septicemia and pneumonia due to a Gram-negative Bacillus, which, in view of the character of the sputum, was most likely Klebsiella pneumoniae. He was consequently given streptomycin intramuscularly and chloramphenicol intravenously. The pneumonia progressed very rapidly, and the patient died a few hours later. After death the cultures of the blood and sputum taken during the last 48 hours of life revealed Pseudomonas aeruginosa.

The following case summary illustrates the suppressive effect of erythromycin against a chronic staphylococcal endocarditis:

CASE 6.—A 10-year-old girl was admitted to the hospital because of persistent fever. She had been previously found to have a blowing precordial systolic murmur, which was thought most likely to be due to an interauricular septal defect. Blood cultures revealed a hemolytic Staph. aureus (M. pyogenes var. aureus). The patient was treated with penicillin and chlortetracycline, without a significant benefit. On the 14th day of illness erythromycin capsules were given orally. There was an inconsistent control of the fever, and after six weeks the capsules were discontinued and coated erthromycin tablets were substituted. During therapy with the tablets, the fever and other evidence of the infection improved, but when the antibiotic was discontinued the fever recurred and the blood cultures became positive. In vitro sensitivity tests revealed the organism to be sensitive to streptomycin and erythromycin but resistant to other antibiotics. As a result of these tests the patient was placed on a combination of streptomycin and erythromycin for a total of six weeks. The streptomycin was given because the in vitro studies demonstrated that it was bactericidal against the etiologic organism. Erythromycin was given in an attempt to prevent the emergence of organisms resistant to streptomycin. During the seven weeks of this therapy the patient was asymptomatic and the blood cultures were sterile. The patient has been observed for a period of six months since discontinuance of all treatment, and there has been no evidence of recurrence of infection.

Other Infections.—Two patients with infections due to Bacterioides funduliformis were treated with erythromycin. The first was a patient with postpneumonic empyema of the right pleural space, and the second was a patient who developed multiple lung abscesses and bilateral empyema secondary to a Bacterioides septicemia. Tube-dilution sensitivity tests demonstrated that the organism isolated from the second patient was sensitive to erythromycin, chlortetracycline, chloramphenicol, and oxytetracycline. Both patients were treated with 400 mg. of erythromycin every six hours. The first patient recovered completely on aspiration drainage and erythromycin therapy. The second patient had a good febrile response to erythromycin, but, because of the persistence of the organism in empyema fluid, chlortetracycline was substituted after two weeks. The latter patient also recovered. Bacterioides was not isolated from the empyema cavity after the first 72 hours in the first case, but in the latter it was cultured from the empyema fluid 11 days after erythromycin had been administered.

Since the original 29 patients, listed in the Table, were treated, two patients with acute gonorrheal cervicitis have been treated. One patient was seen five days after onset, and the other the second day of symptoms. The diagnosis was established by a positive smear and culture. Both patients were treated every six hours for five days. Cultures taken on the third and seventh days after erythromycin was begun were negative. Both patients have remained well.

Undesirable Side-Reactions.—In the treatment of 33 patients with various types of infections the commonest side-reaction was cramping abdominal pain and mild diarrhea. This was not a serious problem in any patient. There was no instance in

which moniliasis became a problem, but in one patient a Pseudomonas infection developed during erythromycin treatment. It was found that the specially coated tablets were tolerated better than the capsules.

SUMMARY

Thirty-three patients with infection due to Gram-positive and Gram-negative cocci were treated with erythromycin.

There was a prompt clinical and bacteriological response in all but three patients with endocarditis and two with staphylococcal empyema.

The dose used was 25 mg. per kilogram per 24 hours. There was clinical evidence that the absorption and antibacterial effect of the coated tablets was more consistent than that of the capsule.

No serious side-reactions were observed, but an occasional patient complained of nausea, cramping abdominal pain, and diarrhea.

The effect of erythromycin was most striking in the management of penicillin-resistant staphylococcal sepsis.

ADDENDUM

Subsequent experience with the administration of erythromycin has confirmed the results reported in this paper. A patient with a staphylococcal bacteremia and meningitis has been treated with large doses of erythromycin, resulting in the sterilization of the blood stream but not the spinal fluid. This observation along with the persistence of infection in empyema cavities reported in this paper. A patient with a staphylococcal bacteremia and meningitis has been not always be relied upon. Erythromycin has also been used unsuccessfully in the treatment of another patient with overwhelming staphylococcal septicemia.

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Progress in Internal Medicine

CARDIOVASCULAR DISEASES

A Review of Some Significant Publications (July 1949-June 1952)

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Concluded from Page 298

VI. PULMONARY HEART DISEASE

IN ACUTE experiments performed on dogs wherein he completely damaged by cauterization the musculature of the right ventricle, Bakos [268] observed no changes in the peripheral venous and systolic and diastolic pulmonary arterial pressures following the injury as compared to the control level of these pressures recorded prior to the cauterization. Because of the continuity of the circumscribing individual ventricular muscle bands, the myocardium of the left ventricle mechanically transmitted its energy to the right ventricle so that the latter chamber passively functioned as an efficient force pump despite complete inactivation of its myocardium. From these studies it seemed apparent that the function of the two ventricles could not be dissociated, since the anatomy of the distinct myocardial bands made inescapable the unified function of both chambers. Kagan,[269] however, has adduced experimental evidence from similar studies that the activity of the ventricles is maintained by quite separate mechanisms; consequently the field remains in flux.

A possible mechanism for the development of pulmonary hypertension and right ventricular hypertrophy has been studied by Harrison,[270] who injected minute fibrin clots intravenously into rabbits for a 20-week period. At the end of this time significant hypertrophy of the right ventricle was evident. One group of the rabbits, killed at this time, was studied by x-ray after radio-opaque injection of the pulmonary vascular tree; no evidence of pulmonary embolization could be found by this technique, doubtless owing to the small size of the embolic particles. By weight, however, the right ventricles in these animals were significantly hypertrophied. In another group of rabbits allowed to survive for 20 weeks after the end of the fibrin clot injections, there was little or no hypertrophy of the right ventricle. The author concludes that at least over the short term tiny emboli exert no mechanical effect but rather induce pulmonary hypertension and secondary right ventricular hypertrophy through spasm, the hypertrophy regressing when the emboli cease occurring. Muirhead and others [271] cite two clinical cases in which the pulmonary vascular sclerosis (endarteritis) might have been considered of the primary type were it not for the presence of numerous occlusive masses within small pulmonary arteries. In one case these masses were either embolic or thrombotic, and in the second they appeared to be proteinaceous; this patient had a marked cryoglobulinemia, and this is the first instance of this condition being reported in association with pulmonary vascular sclerosis. The authors suggest that the term "thromboembolic pulmonary endarteritis" be applied to this form of pulmonary vascular sclerosis. They consider that, rather than a cause of pulmonary endarteritis, the

pulmonary hypertension observed in such cases may be the result of alterations in the nutritional status of the arterial wall secondary to the damage attendant on vascular occlusions and the operation of the repair process as it affects blood vessels. Carroll [272] describes five cases of chronic cor pulmonale resulting from obstruction of the pulmonary artery, in four resulting from embolism and in the fifth apparently secondary to local thrombosis. Yet another case of chronic cor pulmonale due to recurrent emboli to the pulmonary artery has been described by Petch and Camb.[273] Commenting that it is often difficult to distinguish at autopsy between persistent emboli and thrombosis in situ, these workers consider that a number of cases described at autopsy as examples of pulmonary artery thrombosis may actually represent the extension of earlier emboli, since an unexplained or primary thrombosis in such a situation is even less easy to understand. Why this type of embolus persists where others disappear is not clear, but in this case there seemed little doubt that the original obstructions suffered recurrent additions to their substance. In two cases with a necrotizing arteriopathy limited to the pulmonary vascular tree, in one of which primary pulmonary hypertension was present and in the other pulmonary hypertension secondary to mitral stenosis, Symmers [274] reached opposite conclusions. He observed three types of small blood vessel lesions: arteriolosclerosis, comparable to systemic hypertensive arteriolosclerosis; fibrinoid necrosis of the media of small arteries and arterioles, comparable to the arteriolonecrosis associated with malignant systemic hypertension, and arteritis and arteriolitis similar to those seen in polyarteritis nodosa. The author believes that the nature of these lesions and their apparent association with pulmonary hypertension suggests that they are a result of the hypertension and not its cause. This divergence of opinion serves to emphasize the diversity of case material encountered as well as the complexity of the problem. Dresdale [275] and his associates, in a study of primary pulmonary hypertension, comment that arguments against the primary role of vascular changes as the basis for the hypertension are the absence of these findings in some patients with isolated right ventricular hypertrophy proved by catheterization to have pulmonary hypertension and the findings of pulmonary arteriosclerosis unassociated with right ventricular hypertrophy. On the basis of careful clinical and hemodynamic observations these workers believe that an isolated overactivity of the sympathetic nervous system may underly pulmonary hypertension. This opinion stems from the pronounced effect of benzazoline (Priscoline), an adrenolytic and sympatholytic agent, in lowering the pulmonary artery blood pressure and hints at the possible value of sympathectomy in treatment of primary pulmonary hypertension.

Studies by Zimmerman [276] on five patients in whom cor pulmonale developed 8 to 15 years after thoracoplasty showed that all five had marked elevation in pulmonary artery pressure and pulmonary resistance, the pulmonary diastolic pressures ranging from 100 to 500% above normal. In investigations bearing on this work, Denst and others,[277] in a histologic study of the blood vessels in surgically resected tuberculous lungs, found that nearly all specimens showed widespread vessel changes, regardless of whether there had been prior collapse therapy of any sort, and concluded that possibly a toxic factor was responsible.

The pathologic physiology of pulmonary hypertension and right ventricular hypertrophy and failure has been admirably set forth by Cournand.[278] Two principal factors, anoxia and reduction in the capacity of the pulmonary bed, are responsible

for initiating the course of events leading to failure. Anoxia, which is usually operative earlier, induces polycythemia and hypervolemia, which in turn tend to increase the cardiac output, elevate pulmonary artery pressure, and lead then to dilatation of the right ventricle. These factors, together with the direct effect of the anoxia on the strained right ventricular myocardium, stretch the myocardial fibers in excess of optimum, and right ventricular failure follows. The paradox of a high cardiac output in the face of cardiac insufficiency is thus explained by the state of the circulation just preceding the failure of the heart. Because intrinsic myocardial damage is usually limited in this instance, failure is easily reversible with antibiotics, bronchodilators, digitalis, and phlebotomy or its equivalent. In cases in which chronic pulmonary fibrosis, primary pulmonary vascular disease, and chronic multiple embolization of the pulmonary vascular tree are predominant the reduction in capacity of the pulmonary vascular bed is of greater importance. This reduction leads directly to pulmonary hypertension, hypertrophy and dilatation of the right ventricle, and failure with a low cardiac output. Although anoxia may be a precipitating factor in the ultimate onset of outright failure, the situation here is comparable to malignant systemic hypertension and is largely irreversible. Somewhat at variance with the foregoing analysis, Borden and others [279] found the mean arteriovenous oxygen difference in 23 patients with pulmonary emphysema to be similar to that reported in normal subjects. They could find no evidence to indicate that oxygen unsaturation of the arterial blood in emphysema induced an increase in the output of the heart. Their findings indicated that the pulmonary hypertension in emphysema is related to an increased vascular resistance in the lungs.

It would be an injustice to attempt to summarize the fascinating article by McCann [280] on the circulatory function of the respiration. Suffice it to say that the author rejects the concept of the lungs and pulmonary vascular tree as purely passive bystanders in the circulatory drama and presents an ordered picture wherein the lungs function as a check-valve on pulmonary blood flow. From this basis the author speculates provocatively on the genesis of congestive failure, the regulations of coronary blood flow, and apparent discrepancies in Starling's law of the heart. Of especial interest in the light of this analysis is the work of Dack and his group [281] on acute coronary insufficiency due to pulmonary embolism. These workers point out that in addition to mechanical obstruction from the embolus itself there is additional significant reflex obstruction to pulmonary blood flow. These changes result in greatly reduced return to the left ventricle, lowered systemic output and arterial pressure, and frequently the appearance of shock. In the presence of antecedent hypertensive or arteriosclerotic heart disease and cardiac hypertrophy this course of events often leads to coronary insufficiency and in one quarter of the cases studied produced changes indicative of myocardial necrosis or infarction, although in no instance acute occlusion of a coronary artery. In all cases but one the left ventricle was involved, emphasizing the greater severity of the effect of pulmonary embolism on this ventricle.

A reminder of the possible danger of oxygen therapy in chronic lung disease with cor pulmonale is given by Davies and MacKinnon,[282] who noted a sudden increase in cerebrospinal fluid pressure when oxygen was administered in concentrations of 50 to 100%. This increased pressure resulted in myoclonic arm movements in one patient and in coma in another. Similar observations are made by Barach,[283] who notes, however, that if oxygen is given in gradually increasing

concentrations such as 1 liter a minute, with gradual increase of the rate of flow by 1 liter per minute every second or third day, the carbon dioxide of the blood may reach levels as high as 70 to 130 vol. % without respiratory acidosis. Under these circumstances there is adequate time for chlorides to be eliminated in the urine to compensate for the retention of carbon dioxide, and consequently body base can be retained.

A good discussion of air embolism is provided by Cohen and his associates.[284] Arterial air embolism may occur during thoracic surgery or other thoracic procedures, the air entering the pulmonary vein and passing into the systemic arteries of the upper part of the body. Death occurs from coronary or cerebral embolism, and a lowering of the head offers the only possible treatment. In venous air embolism, air enters a systemic vein and reaches the right side of the heart, there obstructing the circulation by an air trap in the right ventricle. Death occurs from this obstruction or from obliteration of the pulmonary capillary bed by air. Treatment consists of placing the patient in the left lateral position, which favors the displacement of the air trap and consequent relief of the circulatory obstruction. A remarkable case of aspiration of the heart in air embolism has been reported by Stallworth, Martin, and Postlethwait.[285] With the patient in moderate Trendelenberg position at the end of an abdominal operation, there was sudden cessation of respiration, circulatory collapse, and sudden appearance of a harsh "mill wheel" murmur and thrill over the entire precordium. Within five minutes a needle was inserted through the chest wall into the right ventricle and several aspirations of about 15 cc. each of air as fine bubbles along with some blood were withdrawn. Before each successive aspiration 15 cc. of whole blood was injected into the ventricular cavity in order to force the remaining air bubbles up to the needle. The harsh heart sounds decreased as the air was removed and ceased when the maneuver was completed. The blood pressure promptly rose to 130/80 and remained at that level. The patient died about three weeks later of generalized polyarteritis nodosa, and at autopsy no scars were found in the pericardium or right ventricular wall at the point where the aspiration was effected.

Reevaluation by Paine and his collaborators[286] of the question of pulmonary edema in patients dying with disease of the central nervous system has led these workers to the conclusion that a purely neurological cause for pulmonary edema, independent of any cardiac mechanism, does not exist. Comparison of the autopsy findings in two groups of patients showed that the incidence of congestion and edema of the lungs was no greater in those who died of neurological disease than in those having no evidence of nervous disorder. Organic cardiovascular disease could be found in the majority of patients with pulmonary edema irrespective of the presence of central neural illness. Stating that every heart, including normal ones, has a "failure threshold," a maximum of work that cannot be exceeded without the development of myocardial failure, the authors suggest that the occurrence of acute pulmonary edema, even in a patient with the occasional seemingly normal heart, may be due, in fact, to heart failure produced by the extreme stress of neurogenic hypertension, cardiac and respiratory arrhythmias, and hypoxia.

After catheter studies of isolated pulmonary stenosis, Silber and his group[287] believe that the dilatation of and the high diastolic pressure in pulmonary arteries in the majority of such cases is caused by maldevelopment of the whole pulmonary artery tree, consisting particularly in a decrease in the total number of medium-

sized and smaller branches of the pulmonary arteries. Viar and Harrison [288] believe that more or less acute distention of the pulmonary arteries may be the cause of the chest pain which may be encountered in association with pulmonary hypertension from various causes. The authors note that glyceryl trinitrate has either no effect or only a minimal palliative effect on pulmonary hypertension; on the other hand, they are unwilling to make a positive diagnosis of angina pectoris in the absence of evidence of striking benefit from glyceryl trinitrate. Glyceryl trinitrate does not aid in differentiating the syndrome from coronary insufficiency or myocardial infarction. Points which aid in the diagnosis of pulmonary hypertensive pain include the recognition from history or examination of any condition capable of causing pulmonary hypertension, a history of long-standing cough, presence of cyanosis, association of the pain with dyspnea, presence of the pain on breathing, variable duration of the pain, clinical evidence of right ventricular hypertrophy, absence of electrocardiographic changes and of evidences of tissue destruction which might accompany myocardial infarction, and striking relief of the pain with oxygen inhalation. The prognosis of the pain in pulmonary hypertension appears to be much better than in coronary disease and in general is that of the underlying disease.

A case of chronic cor pulmonale secondary to compression of the pulmonary artery by a syphilitic aneurysm is recorded by Pearson and Nichol.[289] Although most of these cases terminate by rupture of the aneurysm into the pulmonary artery, death in this instance was from right heart failure. Since approximately one-third of the rare patients with aneurysm of the pulmonary artery die of sudden severe hemoptysis from rupture of the aneurysm, Blades, Ford, and Clark [290] recommend surgical intervention whenever a positive or tentative diagnosis of this condition is made. They report a case in which they ligated and divided the left pulmonary artery proximal to an aneurysm and ligated each branch of the artery arising from the aneurysm. Because of experimental evidence supporting the feasibility of the decision, together with the desirability of leaving the lung in the body as a living, space-filling tissue to help avert compensatory emphysema of the right lung, the left lung was not removed following ligation. Four weeks after surgery the patient's only complaint was slight dyspnea after exertion.

VII. HYPERTENSION AND HYPERTENSIVE VASCULAR DISEASE

Although the jungle of facts and speculation which has sprung up about the etiology of hypertension at times threatens to become impenetrable, nevertheless certain approaches have served at least to widen horizons and perhaps to hit on the path that will ultimately lead out of the wilderness. Renal hypertension is a definite clinical entity, but its mechanisms of action remain obscure. Although the renin, renin-substrate, angiotonin system is known to exist, with the methods at hand these substances cannot be shown to be regularly present in amounts sufficient to increase arterial pressure. The sodium diuresis and zona glomerulosa adrenal cortex enlargement caused in rats by renin and angiotonin point to some as yet unclarified relationship between renal and adrenal mechanisms. Burns and Wakerlin [291] have immunized animals with renal extracts containing renin and have prevented subsequent production of renal hypertension; some of the antisera thus obtained have had a depressor action in animals with renal hypertension, and some of the extracts have immunized against vascular lesions as well. A human instance

of malignant hypertension of seemingly pure renal origin has been described by Goodman.[292] At autopsy in this case there was an old thrombotic occlusion of the right renal artery and there was no arteriolar sclerosis in the right kidney; the left kidney showed malignant nephrosclerosis. From these observations the author concluded that constriction of the renal artery and ischemia of the right kidney preceded the hypertension.

Partial reduction of portal vein blood flow, by means of a Goldblatt clamp, to the point where fatty infiltration of liver cells results, has been shown by Davis and Tanturi [293] in dogs with experimental renal hypertension to lead to a gradual return of the elevated systemic blood pressure to normal levels. Additional partial occlusion of the hepatic artery leads to even more consistent reduction of blood pressure. One possible explanation of these phenomena is that the damaged liver is unable to manufacture hypertensinogen, an essential participant in the pressor reaction in renal hypertension, thus reducing the pressure. An alternative explanation is that the anoxemic liver produces an active vasodepressor material. In this connection the work of Shorr and his associates [294] is of great interest. Studying shock in dogs, these authors have found evidence of the existence of two new vasotropic principles. The vasoexcitor principle (VEM) is formed in the kidney in response to shock and perhaps other stimuli and acts peripherally to sensitize the precapillary arterioles to the action of epinephrine. The vasodepressor principle (VDM) originates in liver, skeletal muscle, and spleen and is instrumental in the circulatory collapse which terminates fatal shock. Confusingly, Page [295] has shown that hepatectomized animals lose their vascular reactivity and die in circulatory collapse. Davies, Olsen, and Schroeder [296] have reported the presence in the blood of hypertensive patients but not in normotensive blood, and more often seen in renal than in endocrine or neurogenic hypertension, of pherentasin, a humoral pressor substance, and have preliminary evidence that another volatile pressor substance is present in the blood of some hypertensive patients, usually in association with higher levels of pherentasin. In view of the lack of correlation between concentrations of pherentasin and the observed diastolic blood pressures of the patients (a sevenfold range of concentrations of pherentasin has been observed at the same level of diastolic pressure), the authors conclude that the explanation of these findings can only be that there are variable amounts of depressor materials in the circulating blood. Evaluation of renal and hepatic interplay, together with the numerous other variables in hypertension, must await further research, but the concept that hypertension may at times stem from an insufficiency of depressor agents, rather than a superabundance of pressor substances, opens avenues of inquiry which may prove most fruitful.

Knowledge has been growing of the part played by the adrenal cortex in hypertension, presumably by way of its hormonal control of electrolytes. Holley and his collaborators [297] have found, despite a wide overlap, a slight but statistically significant higher range and average of serum sodium levels in hypertensive as compared to normal persons. Studying the concentration of sodium and chloride in the sweat of random hypertensive patients, Davies and Clark [298] believe that there exists in some persons a type of essential hypertension in which there is an abnormal resorption of all salt from the sweat, probably mediated through the adrenal cortex, together with clinical signs of hyperadrenocortical function. At the same time their studies seem to show that in the majority of cases of essential hypertension hyper-

activity of the salt-retaining hormone of the adrenal cortex does not play a part. Investigating the relation of elevated blood pressure to the vitamin B_6 group of compounds, Olsen and Martindale [299] have induced hypertension through a pyridoxine-deficient diet in young rats. A significant increase occurred in the adrenal weights of the deficient animals, with a parallel ventricular hypertrophy. On histological examination, no arterial or arteriolar disease could be seen. Restoration of pyridoxine to the diet led to a fall of blood pressure to normal levels. Perera [300] stresses prompt blood pressure rise in hypertensive patients to whom desoxycorticosterone acetate is administered, a response which can be masked by rigid sodium restriction. Cortisone given to patients with renal disease likewise leads to systolic and diastolic rises in blood pressure within a few weeks.[301] The possibility that a metabolic factor may antedate the first signs of overt hypertension is illustrated [302] by a normotensive patient who sustained an increase in arterial tension following desoxycorticosterone administration and who also failed to lose weight during a period of rigid salt restriction. Three months later in this patient a mild persistent hypertension developed for which no renal nor adrenal medullary basis could be found. In observations which may prove highly significant Tobian and Binion [303] have shown that in the renal arteries of hypertensive patients the sodium content is 22% higher and the water content 17% higher than in the arteries of normotensive subjects. There is no evidence to show how much of the increased sodium and water is intracellular and how much extracellular, but the authors imply that the increase may be intracellular. The authors reason that if a sodium and water retention took place in the arterioles similar to that observed in the renal artery, with resultant swelling of the arteriolar wall by roughly 13%, the consequent decrease in lumen size could increase flow resistance by 54%; if this change occurred in all arterioles throughout the body significant hypertension would result. It is not known whether alterations in adrenocortical steroid metabolism play a role in causing the elevated sodium and water in hypertensive arterial tissues, but the improvement seen in some hypertensive patients on a rigid low-sodium diet may stem from diminution of such arterial and presumed arteriolar swelling. Of interest also is the work of Rosenman and his associates,[304] who found that in potassium-deficient rats peripheral vascular reactivity was consistently and significantly reduced as compared with normal rats. The vascular reactivity was measured by the degree of response to the intravenous injection of epinephrine, arterenol (Nor-epinephrine), angiotonin, and renin. These workers further noted that the fall of blood pressure occurring in both normotensive and hypertensive rats subjected to potassium deprivation can be quickly reversed by the administration of potassium, suggesting not only that both the decline in vascular reactivity and blood pressure are specifically due to the absence of potassium but also that the decline in blood pressure itself is due to the changes produced in the peripheral vasculature, changes which are functional in nature and quickly reversible after administration of potassium alone.

More and more, despite the remonstrances of Altschule [305] that parallel findings do not necessarily imply causal relationships, there is general agreement * that the seemingly constitutional personality inadequacies usually demonstrable in patients with essential hypertension are the primary underlying cause of their hypertension.

* References 306, 307, and 308.

Sokolow and others [309] compared 39 college women who had shown elevations of blood pressure on routine initial physical examinations with 39 controls with low normal pressures. The former, or prehypertensive group, were found to be typically more hostile and less well controlled than the normal persons and in general less well equipped to cope with experimental stress. Both Lowy [308] and Wolff [310] have emphasized that the person with hypertension is living in a state of perpetual preparation for action that appropriately should last 10 to 30 minutes but which for him becomes a way of life. As Wolff points out, the preparation for action, particularly aggressive action, raises cardiac output and blood pressure but at the same time leads to renal vasoconstriction, perhaps as part of the general diversion of blood from visceral organs to the organs of offense and defense. This pattern of homeostasis, while of potential value in emergency situations, may possibly result in damage to and perhaps destruction of the organism itself when it can be elicited by inappropriate stimuli and sustained over long periods of time. In contrast to this hyperdynamic response to stress, Wolff further points out that in certain persons quite the opposite to the preparation to fight may occur if defeat seems inevitable; namely, drop in cardiac output and pressure, with resultant giddiness, faintness, fatigue, prostration, and asthenia. Thus there seems to be some basis in fact for the familiar diagnoses of sympathotonia and vagotonia. Vascular hyperreactivity appears to be inherited as a dominant characteristic and occurs more frequently in families with a high incidence of hypertensive disease.

The neurogenic release of energies resulting from conflicts within the psyche appears to involve both the hypothalamic-pituitary axis (a humoral mechanism) and the sympathetic nervous system. In an x-ray study of the hypophyseal area in 100 male hypertensive and a control group of normotensive persons Ziskin [311] noted a slight but definite tendency to increase in the size of the hypophyseal fossa in the hypertensive patients, the increase in size tending to bear a direct relationship to the increase in the blood pressure. Austen and Westphal [312] noted a similar relationship in 53% of hypertensive persons. In a fascinating paper much too detailed for summary here, Findley [313] has argued that a decline or abiotrophy of the hypothalamic nuclei may underlie not only hypertension but most of the symptoms of the aging process as well. Secondary to this hypothalamic decline there occurs atrophy and reduction in numbers of the basophile cells of the pituitary, with consequent preponderance of the eosinophile elements. This imbalance, the theory runs, causes a relative hyperadrenocorticism with Cushing's-disease-like symptoms, including hypertension. The shift in eosinophile-basophile activity of the anterior lobe of the pituitary may also lead to a state of heightened tissue responsiveness to the combined actions of such pressor materials as desoxycorticosterone, progesterone, renin, and epinephrine. If this heightened responsiveness were true, it would again not be necessary to demonstrate increased amounts of pressor substances in biologic fluids of animals and humans with chronic hypertension. On the whole, however, despite the attractive unitarian character of this hypothalamic-pituitary-adrenocortical theory, the weight of evidence points away from hyperadrenocorticism.

On the sympathetic vasomotor side of the neurogenic background of hypertension, it has been assumed that increased vasomotor discharge is the fundamental mechanism in neurogenic hypertension. Relief of essential hypertension by sympathectomy, however, as pointed out by Page and McCubbin,[314] may just as well

be simply the removal of a normally functioning mechanism from the group of normal and abnormal mechanisms which combine to maintain abnormal arterial pressure. Not only is the efferent vasomotor pathway of significance, however. Under appropriate conditions the sinoaortic buffer system may stimulate an increased discharge of the vasomotor center, leading to an increased ganglionic resistance to tetraethylammonium chloride blockade. Clinically it may yet be shown that such a resistance in the human patient may indicate a predominantly neurogenic hypertension which should respond well to adequate surgical sympathectomy. Further, much remains to be learned about the von Bezold reflex system, with receptors in the myocardium and the lungs, which likewise plays a part in vasomotor regulation. Lastly, as Page and McCubbin emphasize, vasomotor control of arterial pressure may be effected not only by stimuli which directly change the caliber of the vessels but also through changes in the capacity of the vessel to respond to usual humoral or nervous influences—in a word, changes in the vascular reactivity. This concept of vascular reactivity, which has lately come into prominence, may be compared in significance to that of vasodepressor mechanisms referred to earlier. Together these concepts open vast new areas to what may prove to be more definitive investigation than the thus far unrewarding search for some pressor agent present in excess in essential hypertension.

The standards of normal systolic and diastolic blood pressure levels have been significantly extended upwards by the extensive statistical analyses conducted by Master and his associates.† On the basis of casual blood pressure determinations on 16,000 factory workers throughout the country these authors conclude that the lower limits of systolic hypertension range from 150 mm. Hg at age 19 to 190 at age 65 and that corresponding lower limits of diastolic hypertension range from 90 to 110. When clinically identifiable malignant hypertension or hypertensions secondary to renal or other diseases are excluded, many persons currently termed hypertensive because of blood pressures above accepted normal levels such as 150/90 may still not be suffering from a specific illness but merely demonstrating the aging process as related to systemic blood pressure. These authors further believe that the association between hypertension and coronary disease with presumed worsening of prognosis by the hypertension has been exaggerated. Even after coronary occlusion the immediate prognosis for those with hypertension is no worse than for those with normal blood pressure, and when evidence of coronary disease, cardiac enlargement, or heart failure is present with blood pressures within the levels under discussion treatment should be directed toward those diagnoses rather than toward the hypertension. Since elevated blood pressures are even commoner in women than in men over the age of 45, the frequently mentioned association of feminine coronary disease with hypertension may be a coincidence. Krane and Perera [317] in a study of a group of patients who died after the age of 60 with hypertension not present before the age of 55 agreed that many instances of hypertension in later life may be due to some basis other than that producing the usual picture of hypertensive vascular disease. In these patients the life expectancy and degree of renal arteriosclerosis approximated those observed in elderly subjects with a normal blood pressure. In another series of 100 patients with abnormal elevation of blood pressure (repeated casual diastolic readings of 90

† References 315 and 316.

mm. Hg or more) discovered not longer than two years following known normal blood pressure, Perera [318] found the average age at onset to be 32 years and the average duration of life 19 years. Twenty-four of the women had pregnancies during this period, and data on these cases suggested that sustained elevations of blood pressure after a pregnancy are indicative generally of some disease antecedent to the pregnancy. An average survival of five or more years may be observed after any single complication of hypertension except in patients suffering cerebral vascular accidents or those demonstrating papilledema or renal failure. In autopsy studies of a large group of persons with essential hypertension, Smith and his co-workers [319] found that the incidence of a significant degree of associated coronary sclerosis was highest (approximately 85%) in patients who had hypertension Groups I and II; in Group IV only 57% had this association. Renal impairment, on the other hand, was directly related to the severity of the hypertension, as was the mean age at death: 62 years in Group I and 47 years in Group IV. A carefully weighed program, avoiding insofar as possible the pitfalls usually surrounding ordinary clinical studies of the natural history and treatment of essential hypertension, has been described and put into practice by Evelyn,[320] and the results of this study will be awaited with great interest.

The numerous evaluations of the efficacy of the sympathectomy procedures for the relief of arterial hypertension continue to result in opinions and emotions ranging from enthusiastic to dejected, with the weight of opinion tending to restrict the field of surgery ever more sharply. On the optimistic or interventionist side, Smithwick [321] reports that observations over a 4- to 12-year period on the first 892 patients in his extensive experience indicate quite clearly that the prognosis for patients with hypertensive cardiovascular disease significantly improves after thoracolumbar splanchnicectomy. Numerically grading hypertensive patients initally according to a useful set of criteria of his own, this author excludes from recommendation of sympathectomy only those persons who on the one hand show minimal or no eye ground changes and no changes in cerebral, cardiac, or renal areas, and, at the other extreme, those with persistent nitrogen retention. Essentially similar conclusions were reached by Hammarström and Bechgaard [322] in a comparison between 251 patients studied after sympathectomy and a selected group of 435 medically treated patients. On the basis of 562 surgically treated persons with hypertension, de Takats [323] employs three major and one minor indications for operation. First, sympathectomy is undertaken in all patients showing the earliest signs of vascular damage in the retina, heart, or kidney, both because the patient has shown vascular vulnerability and because operation at this stage is considered highly efficient in arresting the progress of vascular damage. Second, surgery is indicated for the middle-aged hypertensive patient with diffuse arteriosclerosis and moderately elevated diastolic pressure of 100 to 110 mm. Hg unaffected by medical management; lessening of sudden rises of pressure that may occur with exertion, undue emotion, cold, and posture change is said to give such a patient a better chance of survival than does medical management. The third indication is the rapidly progressive premalignant phase prior to severe renal damage. Finally, in an occasional patient with hypertensive encephalopathy and advanced renal damage, intractable headache may be relieved by a limited one-stage sympathectomy. In assessing renal damage preoperatively by a water-tolerance test the author [324] has found that a patient showing late water excretion and a failure to reconcentrate

urine to raise its specific gravity is usually not improved by surgery, even though preoperative phenolsulfonphthalein excretion and urea clearance studies may be satisfactory.

A vastly more conservative position has been reached by Thorpe, Welch, and Poindexter,[325] based on study of 500 cases of bilateral thoracolumbar sympathectomy for hypertension, followed for periods of up to seven years. Although noting definite decreases in diastolic pressure in a significant number of patients over a fairly prolonged period, together with a reversal or improvement in some patients of other hypertensive manifestations, these authors found no significant difference in survival rate between their patients in hypertensive Groups I, II, and III and a comparable medically treated group. A significantly higher survival rate was apparent in the operated patients in Group IV. The authors conclude that thoracolumbar sympathectomy is the most effective form of therapy available for palliation of hypertension of patients in Group IV (with the exception of certain severely injured patients) and for selected patients in Group III. Similar evidence of the value of surgical intervention in the more advanced cases of hypertension is provided by the follow-up study by White, Dimond, and Williams[326] of 100 hypertensive persons seriously affected either by the hypertension or by coronary disease, as shown by the presence of an important cardiovascular complication (myocardial insufficiency, cerebrovascular accident, past myocardial infarction, or angina pectoris). In this series the sympathectomized patients showed a distinctly better status both in mortality and morbidity than did the nonsympathectomized patients. As the authors point out, the hard facts of mortality and morbidity provide more impressive evidence of the beneficial effects of sympathectomy in certain cases than the usual method of studying the effect of surgery on blood pressure alone in cases in which important complications do not exist. Keith and his associates[327] agree that greater well-being and perhaps an increase in life expectancy occur after surgery for malignant hypertension but conclude that surgically treated patients with benign hypertension, although showing superior symptomatic results, fail to show any statistical difference in mortality rates when compared to a medically treated group. Least enthusiastic of all, Platt and Stanbury[328] believe that the satisfactory results reported by others may be attributed to insufficient preoperative evaluation of the patient with benign hypertension, failure to appreciate the great variability of blood pressures in these patients, and unawareness of the relatively good prognosis in milder cases. The authors doubt that the blood pressure height is an accurate index to the severity of the basic disease process or its prognosis and find little to suggest that sympathectomy in any way alters or reverses the basic disease process of which hypertension is but one effect. They conclude that great care should be used in choosing subjects for the operation and the sympathectomy should rarely be advised.

A most unusual case of hypertension secondary to polyarteritis nodosa has been recorded by Horne and his collaborators.[329] Following sympathectomy their patient had relief of hypertension and was in good health six years later, at the time of the report, leading the authors to assume that the etiological factor causing the polyarteritis was dissipated in some fashion. An additional point of interest was the observation that when the patient's blood pressure fell below 100 mm. Hg for three days he was free from pain in his limbs but with a rise in blood pressure to 136/72 on the fourth postoperative day there was a coincidental return of pain.

It is suggested that the systolic blood pressure, by producing sudden thrusts and stretching the walls of the necrotic arteries, is an important factor in the production of pain in diseases associated with arterial necrosis. A possible or at least partial explanation for the recurrence of hypertension in many patients after sympathectomy is provided by Randall and others,[330] who demonstrated the presence of accessory vasoconstrictor fibers in the sympathectomized hind limb of dogs. At autopsy careful dissection of the spinal nerves and the intercommunicating rami of the lumbar segments showed ganglion cell groups whose postganglionic fibers passed directly along the ventral primary ramus without entering the paravertebral ganglion chain. These cells and their fibers, and presumably similar ones at levels higher in the cord, would not be severed by ganglionectomy and therefore provide a possible anatomic basis for residual vasoconstrictor activities. Development of hyperpyrexia during a heat wave in two patients who had recently undergone extensive bilateral thoracolumbar sympathectomies emphasizes that, because of the abolition of most of the sweating mechanism, these patients are unusually susceptible to high environmental temperatures.[331] Finally, in connection with sympathectomy, Adson [332] has recorded the relief in two hypertensive patients of recurrent transitory hemiparesis by bilateral removal of the superior cervical sympathetic ganglia. By thus interrupting vasomotor fibers coursing along the internal carotid artery, further presumed angiospasm of the artery and consequent temporary hemiparesis were prevented.

The potentialities of subtotal adrenalectomy, both as an adjunct to and as an alternative to sympathectomy, have been explored by Wolferth and his group.[333] In some cases subtotal adrenalectomy alone, removing more than 90% of the adrenal tissue and creating at least a minimal degree of adrenocortical insufficiency, was enough to reduce arterial blood pressure from extremely high levels to a normal range, relieving heart failure and improving renal plasma flow and cerebral vascular resistance. The combination of subtotal adrenalectomy and sympathectomy, however, seems more promising. The results of the logical extension of this thinking to bilateral total adrenalectomy have been recorded in 15 patients suffering from malignant hypertension or chronic nephritis by Harrison, Thorn, and Criscitiello.[334] All the patients had failed to benefit from strict medical treatment and were considered too ill to undergo sympathectomy, life expectancy being limited to a few months in all cases. Four of the patients subsequently died of heart disease, three of renal disease, and one of unrecognized Addisonian crisis. The procedure proved valuable in six of the patients, with not only reduction of symptoms, including anxiety, but also distinct improvement in signs, such as decrease in heart and liver size, increase in vital capacity and exercise tolerance, and loss of edema. A sustained diuresis of sodium chloride and water was noted, together with a moderate to excellent drop in blood pressure in all six. As commented by Huggins and Bregenstal,[335] subtotal adrenalectomy leaves the possibility that the remaining glandular fragment may hypertrophy and renew the original hypertension or atrophy completely with ensuing Addisonian problems. With bilateral total adrenalectomy the latter problems are obviously created at once. Adrenal surgery for hypertension is still clearly in the investigational stage, and its ultimate usefulness, if any, seems limited to rather desperate situations. Further uncertainty is introduced by the demonstration by Turner and Grollman [336] that bilaterally adrenalectomized nephrectomized dogs maintained on peritoneal lavage for 40 days without hormonal

therapy became hypertensive. Postmortem findings in heart and blood vessels were like those in animals with nephrectomy alone, and the authors concluded that the adrenals do not determine the development of hypertension.

In connection with adrenal aspects of hypertension, Davis and his co-workers [337] have shown in a series of hypertensive dogs that thiocyanate therapy causes depletion of lipid granules in the adrenal cortex, most marked in the zona glomerulosa. The granules reappear when the medication is withdrawn, and bilateral thoracolumbar sympathectomy seems to increase the effect of the thiocyanates, suggesting that a combination of sympathectomy and the thiocyanates might be more effective in lowering the blood pressure than either procedure alone. Clinically, Pines and Perera [338] have studied average daily urine sodium excretion under controlled conditions and have shown that with thiocyanate administration the average urine sodium excretion rises 15% in a normotensive group and 33% in a hypertensive group. They conclude that thiocyanates may exert a depressor effect through mechanisms similar to those whereby rigid salt restriction relieves hypertension.

Numerous evaluations of the role of the low-sodium and the rice diets in the management of hypertension confirm the effectiveness of such dietary regimens in certain persons on a trial and error basis.‡ Careful metabolic studies contrasting the effects of addition of salt-free proteins or varying amounts of sodium chloride to the rice diet lead to the conclusion that, except for patients with azotemia, the rice diet provides nothing but an unduly restrictive low sodium program. Of interest in this connection is the study by Nye and Forrest [347] of 103 aged aborigines in the Cape York peninsula of Australia. Despite their age, these natives evidenced a remarkable lack of hardening of the arteries and not one instance of hypertension. The diet in this area is composed chiefly of protein, but there is no contact with salt whatever. Contrary to earlier misgivings, significant derangements of electrolyte metabolism, even on the rice diet, have been noted in only 5% of persons with normal renal function. In the overwhelming majority, according to Peschel and Lohman-Peschel,[348] the only changes are a moderate drop in chloride and increase in bicarbonate occurring during the first few weeks of treatment, with sodium, potassium, and total ionic concentrations essentially unchanged. The almost insuperable difficulty of effective application of the diets for sustained treatment stems from the extremely low critical tolerance level of sodium intake, with respect to hypertension, and the more or less prompt return of hypertensive manifestations with even slight sodium intakes above this critical level. The effort of will required of most patients to keep sodium intake to the necessary minimum in most instances proves too great for long endurance. In the words of Job (vi: 6-7):

> Can that which is unsavoury be eaten without salt, or is there any taste in the white of an egg? My soul refuseth to touch them; they are as loathsome meat to me.

Of outstanding interest in the field of hypertension during the past few years have been the development and clinical trial of the several pharmacologic vasodepressor agents. Of those earlier in the field, the ergot and veratrum alkaloids merit some attention. Using dihydroergocornine, Freis and his associates [349] showed that hydrogenated ergot alkaloids could abolish the pressor response to the Valsalva maneuver, prevent the vasopressor overshoot in hypertensive patients occurring on rapid sitting up, inhibit the cold pressor response, and increase peripheral extremity

‡ References 339, 340, 341, 342, 343, 344, 345, and 346.

circulation accompanying a drop in blood pressure. Bradycardia is commonly produced, seemingly due at least in part to inhibition of the sympathetic cardioaccelerator mechanism. In contrast, the dehydrogenated ergot alkaloids show only slight adrenolytic properties insofar as cardiovascular reactions to injected epinephrine are concerned, suggesting a central rather than a peripheral sympathetic blocking effect. Time has largely borne out the authors' conclusion that these sympatholytic agents have fundamental limitations in the treatment of essential hypertension, despite optimistic reports by Kappert [350] and by Tandowsky.[351] Using a combination of equal amounts of dihydroergocornine, dihydroergocrystine, and dihydroergokryptine (C. C. K.-179), Dupy and his co-workers [352] conclude that clinically this compound has no practical application in the management of persons with essential hypertension because of the low incidence, minimal degree, and short duration of hypotensive effect.

Experience with veratrum viride and its derivatives has followed a course generally similar to that with the ergot alkaloids. Using both veratrum viride and veriloid (a mixture of the active hypotensive alkaloids of the crude drug), Wilkins and his associates,§ by a meticulous regulation of dosage to minimize nausea and vomiting, were able to produce a definite drop in both systolic and diastolic pressures in a group of patients, with some improvement in signs and symptoms in some of the group. Kauntze and Trounce [355] found that veriloid by mouth lowers the blood pressure in about two-thirds of hypertensive patients but that in half of this number the hypotensive dose so closely approaches the toxic level that daily use of the drug outside of the hospital is not practical. Even in the roughly 30% in whom the drug is a satisfactory hypotensive agent, the dosage requires continuous supervision and the cooperation of an intelligent patient, since sensitivity may change after months of administration. On the whole it seems likely that toxic effects are an inseparable expression of the hypotensive qualities of the ester alkaloids in veriloid. For the immediate vigorous treatment of severe forms of hypertensive disease, slow intravenous infusion of veriloid has been shown to be of some value by Stearns and Ellis.[356] Despite encouraging symptomatic responses, however, the survival data for the patients studied did not indicate that the course of hypertensive disease of the severe types was materially altered by such therapy. On the debit side, Barrow and Sikes [357] have deplored the widespread recommendation and use of the noxious alkaloids of veratrum viride, because of their relative ineffectiveness. McNair and his group,[358] administering veratrum viride orally to a group of 22 patients in maximum tolerable doses, failed to show any significant change in blood pressure or pulse rate during the treatment. These workers believe that a rapid development of tolerance to the drug may explain their observations. The purified veratrum alkaloid protoveratrine, administered intravenously, has been shown by Meilman and Krayer [359] to produce a significant fall in blood pressure lasting one to three hours at doses free from serious side effects. The short duration of action and the necessity for parenteral administration make this approach too cumbersome for practical clinical application. Recently Currens, Myers, and McGinty [360] have reported oral administration of protoveratrine to 24 patients for periods ranging from 6 to 30 months, with improvement in most instances in both the blood pressure levels and the accompanying symptoms. Although the margin between the

§ References 353 and 354.

effective and toxic dosages of the drug is slim and requires adjusting at unpredictable intervals, protoveratrine may find a place in the long-term treatment of hypertensive vascular disease in some patients.

Certain others of the earlier blocking agents of seemingly great promise have proved on further experience to have little or no usefulness in the therapy of hypertension. The tetraethylammonium halides to produce adequate sympathetic blockade must be given in doses exceeding the limits of comfort or safety, and even then the duration of action is for a few hours only.[361] Contradicting initially optimistic reports, Dumoulin[362] found tetraethylammonium bromide of very limited practical value in the study and treatment of the toxemia of pregnancy, chiefly owing to excessive variability of the response. Similarly with regard to Dibenamine (N-N-dibenzyl-β-chlorethylamine), Wunsch and his associates[363] have found the drug contraindicated in the treatment of ambulatory hypertensive patients, not only because of its toxicity but also because of marked and prolonged orthostatic hypotension. The only clinical application of Dibenamine, and then not as a first choice, may be its use in hypertensive encephalopathy, to tide the patient over an acute episode in hopes of obtaining sufficient improvement to permit sympathectomy.

Attention is currently centered almost exclusively upon the hexamethonium salts and hydralazine (1-hydrazinophthalazine; Apresoline) or a combination of these two compounds or their analogues. Much of the early clinical work was reported by Smirk and his co-workers.|| Summarizing this experience, Smirk states that observations on 130 hypertensive patients of varying types included those with fixed and labile essential hypertension, malignant hypertension, hypertension remaining or recurring after sympathectomy, the hypertensions of chronic nephritis and nonnephritic renal damage and acute toxemia of pregnancy, and the hypertension remaining after toxemia of pregnancy. Methonium halides reduced blood pressure in all these patients during the action of the drug, regardless of the pathogenesis. In most severely hypertensive patients systolic pressure decreases of 60 mm. Hg or more, and lesser reductions of diastolic pressure, could be effected without causing other than minor symptoms. In a few cases blood pressure reductions although present were inadequate; in others, reductions up to 120 mm. Hg of systolic pressure were noted, sometimes without discomfort. In most types of hypertension, effective reduction of blood pressure was possible without important side effects. The action of methonium salts is greatly enhanced by salt-poor diets providing a daily intake of 0.2 gm. of sodium or less; under these circumstances one half or one third of the original dose produces the full effect. Continued administration of hexamethonium leads to drug tolerance, but after some months the drug dosage becomes stable and tolerance does not interfere with continued treatment. The principal toxic symptoms with methonium salts are faintness and lassitude, but these occur only when blood pressure fall is excessive. In contrast to the one patient out of three who obtains substantial blood pressure remission without toxic symptoms using veratrum alkaloids, almost all patients can take methonium salts at some level which provides practical reduction of blood pressure without excessive toxicity. Commenting further on toxicity, Freis and his collaborators have found that postural hypotension diminishes in severity with prolonged treatment with hexamethonium and that constipation and occasional paralytic ileus from gastrointestinal atony and

|| References 364 and 365.

rare difficulty in urination can usually be circumvented. There is general agreement that more predictable results can be obtained from subcutaneous injections of hexamethonium than by use of the oral route. Studies on the hemodynamic effects of hexamethonium in man lead Freis and others ¶ to the conclusion that the autonomic blockade following hexamethonium does not produce a uniform decrease in peripheral vascular resistance. The sympathetic vasoconstrictor nerves appear to be of great importance in maintaining vascular tone in regions such as the hands and the feet, where hexamethonium leads to a manyfold increase in blood flow, but of much less importance in other areas such as the kidneys and muscles, where the drug causes no change or perhaps even a decrease in blood flow. Crumpton and Murphy [368] have shown that following a significant blood pressure reduction induced by hexamethonium the cerebral and coronary volume flows are maintained during the period of blood pressure reduction.

As an antihypertensive agent, hydralazine gives particular promise owing to the demonstration by Reubi that at the same time that blood pressure is moderately lowered in hypertensive patients by this compound, there is an effective renal plasma flow increase. Extensive clinical studies by Schroeder [369] have shown that hydralazine is relatively nontoxic and can be administered for several months with some reduction of blood pressure and without harmful renal effects. In only 2 patients out of 50, however, was there convincing evidence that life was prolonged by use of the drug. Side actions are usually not serious enough to contraindicate a therapeutic trial. Severe headaches may appear but usually diminish despite continued administration of the drug. Tachycardia and postural hypotension may also diminish as blood pressure becomes stabilized at lower levels. Nausea and vomiting and other gastrointestinal symptoms are seen especially in patients who have been sympathectomized. Schroeder concludes that the members of the hydrazinophthalazine group are the most effective agents against hypertension so far encountered for practical clinical use but that they are only a partial answer to the problem. Johnson, Freis, and Schnaper [370] are in general agreement with the above conclusions but emphasize that frequent administration of the drugs usually leads to the rapid development of tolerance. For this reason persistent reduction of arterial pressure over prolonged periods is rarely obtained with hydralazine alone. These authors agree with Schroeder [371] that intermittent or alternate doses of this drug and hexamethonium minimize the occurrence both of side effects and of tolerance and permit a greater and more sustained reduction of blood pressure than when either agent is used alone. All observers stress that serious accidents may occur with improper understanding and usage of these potent chemicals and urge that all patients be started on small doses with close clinical and laboratory supervision under hospital conditions. Long-term effects remain to be determined, and it is probably well to restrict the use of these drugs to severe cases requiring immediate reduction of blood pressure. An excellent summary of the uses and precautions to be observed with hexamethonium salts and hydralazine has been provided by Grimson and his co-authors.[372]

A new sympathetic blocking agent, 688-A (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride) has been found by Moser and his associates [373] to give on oral administration blood pressure responses comparing favorably with

¶ References 366 and 367.

the results obtained in patients following surgical sympathectomy. The initial series is small, however, and further evaluation of this preparation is required. Schroeder[374] has found that a number of sulfhydryl compounds possess a hypotensive effect on rats with renal hypertension. Pressor amines such as artereno and angiotonin are rendered inactive in rats previously prepared by intravenous injections of sulfhydryl substances. The possible application of these findings to the treatment of human hypertension has yet to be determined. Moderate to marked reductions in both systolic and diastolic pressure levels are reported by Vakil[375] following the use of a preparation from Rauwolfia serpentina, a shrub extensively used pharmacologically in India. This drug is said to produce vasodilatation through its action on the vasomotor center and in addition has some sedative action on the cerebrum. Page[361] has provided a reminder that pyrogens may sometimes be very effective in the treatment of malignant hypertension, in many patients definitely reversing the hemorrhagic arteriolitis. Arterial pressure may rise almost to original levels after discontinuance of treatment, but the malignant syndrome apparently does not return. The wholly negative prognosis of hypertension amply justifies the usual three to four months of harsh pyrogen treatment required for improvement. In the experience of Benchimol and Dias Carneiro,[376] however, the miseries of pyrogen therapy are not compensated for by the short duration of improvement observed in their small series of patients.

Because of the potential curability of pheochromocytoma, interest in the diagnosis and control of this tumor by pharmacologic agents remains far out of proportion to the numerical frequency of its occurrence. Of the provocative tests aimed at inducing a sudden discharge of pressor substance into the circulating blood, with resultant paroxysmal hypertension, the intravenous injection of histamine appears to be the most reliable. Of the compounds which lower blood pressure by competitive inhibition of tumor pressor substances, piperoxan hydrochloride (Benzodioxan) has had the widest application and is considered generally effective against both epinephrine- and arterenol-secreting tumors.# More recently Grimson and his associates[379] have used the adrenolytic and sympatholytic drug phentolamine (Regitine; 2-[(m-hydroxy-N-*p*-tolylanilino)-methyl]-2-imidazoline) in both the diagnostic study and operative control of pheochromocytomas and have found this compound preferable to piperoxan because of the simplicity of the test, the minimal side effects, and the easily recognizable, typical long-lasting hypotension of a positive test. Iseri and his co-authors concur.[380] Apart from the occasional severe untoward reactions,[381] which have included excessive hypertension, acute pulmonary edema, and extreme hypotension with consequent prolonged anuria, the major factor hampering the confident use of provocative and inhibiting pharmacologic agents has been the occasional false positive and negative test recorded with all of the drugs which have received any substantial clinical trial. Examples include false positive tests obtained with piperoxan in patients with primary anterior pituitary adenoma with hypertrophy of both adrenals,[382] chronic pyelonephritis and marked arteriolar nephrosclerosis,[383] and chronic glomerulonephritis with hypertensive encephalopathy.[384] Meilman[385] reports a false positive result using a N,N-dibenzyl-β-chloroethylamine (Dibenamine) congener in a patient with advanced essential hypertension. False negative studies following the use of piperoxan[386]

References 377 and 378.

permit of two theoretical explanations. Certain tumors may so overload the circulation with pressor substances that the inhibiting agent given in customary amounts may be insufficient to produce a clinically demonstrable fall in pressure. On the other hand, other pressor mechanisms, possibly renal, set in motion by prolonged hypertension secondary to the pheochromocytoma, may maintain hypertensive blood pressure levels despite adequate inhibition of circulating epinephrine or arterenol during the test. In view of such uncertainties, Anderson and others [387] conclude that a battery of pharmacological tests has a definite and useful place in the diagnosis of pheochromocytoma and Calkins and his collaborators [378] point out that in a few instances the decision as to surgical exploration or medical management of a doubtful case of pheochromocytoma must be made on clinical judgment alone.

In reviewing the renal manifestations of pheochromocytoma, Fertig and his co-workers [388] emphasize that during an attack there may be oliguria or anuria, with albumin and casts in the urine, and azotemia. Consequently, any case with "paroxysmal nephritis" accompanied by paroxysmal hypertension should arouse suspicion of adrenal medullary tumor. Goldzieher and his associates [389] have described an interesting case in which there were recurrent paroxysms of hypertension showing negative reactions to tests with adrenolytic drugs and the patient was found at operation to have coarctation of the abdominal aorta. Whether the anatomical lesion was the cause of the clinical picture or purely coincidental could not be determined, but in either case the pathogenesis of the paroxysmal hypertension was obscure. Aronson, Stern, and Cohlan [390] have reported an example of an unusual syndrome in a child of 8, characterized by paroxysmal hypertension and vomiting. Administration of piperoxan was followed by a drop in blood pressure, but exploratory laparotomy failed to discover tumor tissue. Certain other autonomic manifestations in this and other patients led the authors to believe that the syndrome is the result of unusual lability of the autonomic nervous system and is quite unrelated to pheochromocytoma.

VIII. CARDIAC ARRHYTHMIAS

The outstanding recent contributions to further understanding of the atrial arrhythmias have stemmed from the investigations of Prinzmetal and his able group.* Using a high-magnification high-speed (3,000 frames a second) motion picture camera capable of slowing the heart rate approximately 200 times when projected at 16 frames a second, together with a cathode ray oscillograph permitting high speed amplification and recording of cardiac potentials from multiple esophageal and limb leads, these workers have accumulated a vast body of data which they feel refutes the classic circus theory of atrial arrhythmias and in its place establishes a unitarian theory which explains all atrial arrhythmias as varying atrial responses to varying rates of stimulation by a single ectopic focus. In the case of atrial fibrillation, however, no rhythmicity whatever can be demonstrated. In the photographs the spontaneously fibrillating auricle in human subjects shows a constant fluctuation of a multitude of minute contractions and dilatations occurring asynchronously throughout all portions of the auricles. Because of the rapidity and irregularity of the contractions the silhouette and surface configuration of the auricles are constantly changing. On closer examination, two principle types of

* References 391, 392, and 393.

waves are described. "M" or microscopic activity is that of contracting muscle segments as small as 0.2 to 0.8 mm. in diameter, which can be seen to be contracting asynchronously at rates generally between 800 and 1,500 per minute. "M" activity is diagnostic of atrial fibrillation, since nothing similar is to be seen in any other of the atrial rhythms. In addition, macroscopic "L" waves occur simultaneously with and superimposed on the sea of microscopic "M" contractions and dilatations. The "L" waves arrive at a relatively slow rate, of approximately 400 to 600 a minute, and likewise appear to be independent of the ectopic focus. They arise at various sites on the auricle and travel in various directions regardless of the site of stimulation from which the arrhythmia is produced. On the basis of these and other detailed observations, the authors conclude that atrial fibrillation is a chaotic heterorhythmic disturbance in which there is no element of circus movement.

The authors' studies show that when the auricles are electrically stimulated at gradually increasing rates certain manifestations of conduction failure appear before the fibrillation threshold is reached, grow progressively more pronounced, and finally culminate in the chaotic mechanical and electrical activity characteristic of atrial fibrillation. As the rate of stimulation increases there apparently develops incomplete conduction recovery, presumably in good part owing to the shortening of diastole attendant upon the shortened cardiac cycle. Atrial fibrillation results when the rate of discharge from the ectopic focus reaches a level at which conduction is so impaired and diastole so short that the atrium is unable to recover from one contraction and excitation process rapidly enough to receive and conduct the succeeding wave in a coordinated fashion. Administration of quinidine to the fibrillating atrium slows the rate of discharge from the ectopic focus and thereby produces an improvement in atrial conduction, owing to the slower rate, which outweighs the direct conductivity-depressing action of the drug. Under these conditions the "L" contraction and relaxation waves in the fibrillating atrium gradually become stronger and travel greater distances. The "M" activity progressively diminishes in rate and exhibits increasing coordination. As the atrial rate drops below the fibrillation threshold, the "M" activity disappears and the waves are seen to initiate from a single site and travel across the entire contractile surface of the atrium. At this point electrocardiographically the chaotic pattern of fibrillation is often replaced by the regular and often symmetrical atrial deflections of flutter and tachycardia, and finally by normal sinus rhythm.

As between atrial tachycardia and flutter, the authors feel that the various electrocardiographic and therapeutic differences between the two rhythms are related actually to differences in atrial rate and do not indicate a fundamental difference in mechanism. Both are characterized by the discharge of impulses from an ectopic focus at a rate greater than the rate of discharge from the sinus node and lower than the fibrillation threshold. Within this rate range the characteristics of tachycardia tend to appear at slower atrial rates while those of flutter appear most frequently at rapid rates. In man and experimental animals no sharp line of demarcation exists between tachycardia and flutter.

In a study of 84 patients with atrial fibrillation, some permanent and some transient, in whom there was no other evidence of heart disease, Phillips and Levine [394] restored regular rhythm with quinidine in almost 90% without any untoward complications. Although the hearts of some of the patients subsequently relapsed into fibrillation, the maintenance of regular rhythm on the average was

much longer than in patients with organic heart disease whose condition had been reverted with quinidine. Dramatic therapeutic responses were obtained in those of the group showing advanced congestive heart failure, all symptoms and signs of failure disappearing after reversion to normal rhythm. The authors conclude that atrial fibrillation itself may produce cardiac dilatation and progressive cardiac failure in patients who otherwise have normal hearts and is therefore a truly reversible type of heart failure. Very similar results and conclusions are reported by Goldman,[395] in a study of 80 patients for whom he used orally administered quinidine for the control of fibrillation, and by Yount and others,[396] who report on a series of 155 patients with chronic atrial fibrillation. A reminder of the frequent association of hyperthyroidism and atrial fibrillation is given by Bortin and his group,[397] who studied 55 patients with atrial fibrillation without overt hyperthyroidism by means of radioiodine excretion and protein-bound iodine determinations. Eight cases of masked thyrotoxicosis were discovered, and the authors recommend that thyrotoxicosis should be excluded in all cases of atrial fibrillation by the use of these methods.

In a recent pithy survey of the management of established atrial fibrillation, Brown [398] states that whenever a rapid ventricular rate is present, with or without congestive failure or evidence of coronary, cerebral, or peripheral ischemia, digitalis is the drug of choice. With the rapid rate under control and underlying factors treated, consideration can then be given to the use of quinidine to restore normal sinus rhythm. In patients with atrial fibrillation who show a slow ventricular rate, digitalis may be used for the control of heart failure and should be given if quinidine is to be used. This is owing to the fact that most patients with atrial fibrillation who are given quinidine show a progressive slowing of the atrial rate to the point of atrial flutter with concurrent atrioventricular conduction improvement and, as a result, the ventricular rate rises. Prior administration of digitalis tends to prevent the development of such rapid ventricular rate as otherwise might require the discontinuance of the quinidine. The major improvement derived from a normal sinus rhythm is the slower ventricular rate. There is less rise in ventricular rate in response to exercise with normal sinus rhythm than with fibrillation, even when the latter is well controlled with full digitalization. There is also a much more adequate increase in cardiac output during exercise in patients with a normal sinus rhythm than with atrial fibrillation.

A certain hazard attends all quinidine therapy. A case of thrombocytopenic purpura due to allergy to quinidine is described by Hirsch and Dameshek.[399] At one point in this case readministration of quinidine was demonstrated to be accompanied by a drop in platelet count from 1,000,000 to approximately 50,000 per cubic millimeter within 14 hours after intake of a sufficient amount of quinidine. Since the life span of the platelet is believed to be between two and seven days, such rapid reduction of their number suggests that some active destructive process must have occurred, the nature of which remains obscure. Withdrawal of the quinidine in each instance permitted rapid return of the platelet count to normal. Two cases of febrile hypersensitivity to quinidine by mouth are reported by Berley and Saland,[400] and Taylor and Potashnick [401] report a quinidine-induced exfoliative dermatitis, which disappeared with quinidine cessation and reappeared when the drug was resumed. Massive tolerance of quinidine, on the other hand, is demonstrated by the patient of Bell, Bradley, and Hurxthal,[402] who twice received 1.8

gm. of quinidine intravenously over brief periods in efforts to control a persistent tachycardia and who on a third occasion was given 3.2 gm. intravenously over a period of four hours. Toxicity to the point of coma, irregular respirations, cyanosis, vascular collapse, and urinary suppression followed. The patient recovered, however, and was not troubled further by the tachycardia for the duration of the observation period. The authors state that the intravenous dosage of quinidine may vary, not only from patient to patient but also from time to time within the same patient, and they advocate that when quinidine is used intravenously for the treatment of a paroxysmal tachycardia it should be given in a dose large enough to terminate the tachycardia. Evidently some judgment is required here in order not to terminate the patient simultaneously. As pointed out by Sokolow,[403] the risk of the disease should be weighed against the risk of the treatment, and, if the former is great, the risk should be taken honestly. The calculated risk is justified whenever, in a physician's opinion, significant benefit may be derived from restoration of normal rhythm.

In the treatment of paroxysmal supraventricular tachycardia, Barrow [404] has had surprising success with lanatoside C, stopping the arrhythmia in every one of 26 patients within one and one half hours after intravenous administration in doses ranging from 0.8 mg. to 2.0 mg. and averaging 1.2 mg. There were no significant toxic symptoms. In atrial flutter digitalis is the drug of choice for patients with serious organic heart disease or cardiac decompensation or for those in which there are specific contraindications to quinidine, according to Herrmann and Hejtmancik.[405] The digitalis acts by instituting atrial fibrillation, which reverts to sinus rhythm on its withdrawal, particularly if quinidine has been given. Even in refractory cases or those in which permanent atrial fibrillation is established the slow ventricular rate maintained by digitalis provides for more adequate cardiac function. In selected patients without cardiac decompensation or grave organic heart disease, especially if the flutter is of short duration, orally administered quinidine alone may prove effective in restoring sinus rhythm. Combinations of quinidine and digitalis together are less effective than either alone or in sequence but appear desirable whenever flutter occurs in acute myocardial infarction with cardiac decompensation or when 1 : 1 rhythm has once developed with quinidine alone. Bloomfield [406] emphasizes in connection with flutter that it is not possible to predict with assurance what will be the outcome in treatment with digitalis, inasmuch as either regular rhythm or fibrillation may sooner or later appear or flutter may remain unchanged except for increasing block. If prompt restoration to normal rhythm is desired, the use of quinidine must be seriously considered. Further discussion of the numerous agents useful in the control and prevention of especially supraventricular arrhythmias may be found in the excellent reviews by DiPalma and Schultz [407] and by Linenthal and Freedberg.[408]

An effective surgical relief for the occasional case of resistant atrial paroxysmal tachycardia has been provided by White and Bland,[409] who performed bilateral sympathetic ganglionectomy, removing the chains from the stellate down through the fourth or fifth thoracic ganglia. Removal of shorter lengths of the chain or simple section of the cardioaccelerator nerves is likely to be followed by regeneration and return of the arrhythmia. In one instance paroxysmal atrial fibrillation was also stopped by this operation. A more heroic approach is that of Steele,[410] who records successful treatment of persistent anxiety, tachycardia, and raised

basal metabolic rate, unresponsive to other methods of treatment, by bilateral prefrontal leucotomy. During a year of follow-up the patient had no relapse of his arrhythmia and his general personality was distinctly improved.

In three patients who had left bundle branch block associated with coronary heart disease, Levy [411] was able to eliminate the conduction disturbance by administration of oxygen inhalations. The author emphasizes that the early use of oxygen may prevent irreversible changes in the conduction tissue induced by anoxia. An interesting case of left bundle branch block with spontaneous remission after at least three years' duration has been described by Myre and Fuller.[412] In a review of a consecutive series of 452 cases of right or left bundle branch block observed in office practice over a period of 30 years Vazifdar and Levine [413] found 31 instances of benign bundle branch block in persons who had no other subjective or objective evidence of heart disease. No definite cause for these blocks could be determined, and the patients remained well during follow-up periods ranging from 5 to 29 years. The authors state that this type of bundle branch block is harmless and that the patient should be instructed to continue a normal existence.

A possible explanation of the Wolff-Parkinson-White [414] syndrome has been offered by Kisch, based on his extensive investigations of the hearts and electrocardiograms of several types of birds. Stating that in each of the birds studied a well-developed atrioventricular conductive system is present and that in each case electrocardiographically the subepicardial muscle mass is activated before the subendocardial part, the author asserts that the only possible explanation is that the stimulus along the fibers of the conductive system reaches the subepicardial heart muscle earlier than the subendocardial. He considers it no less logical to suppose that occasionally in a human being a short cut of the stimulus conduction is effected by fibers of the conductive system which reach certain subepicardial parts sooner than the normal conductive fibers reach the subendocardial muscle. Such a condition might be stable and work as a steady mechanism, or it might work intermittently only and occasion a transient Wolff-Parkinson-White syndrome. In such an explanation there is no need to call upon the still unproved physiologic effect of a bundle of Kent. A curious case of Wolff-Parkinson-White syndrome associated with dextrocardia and consequently electrocardiographically misinterpreted as a myocardial infarction has been recorded by Bartholomew and Burchell.[415] Report of a 20-year follow-up of one of the earliest described cases of Wolff-Parkinson-White syndrome, by Malinow and Langendorf,[416] attests to the benign nature of this condition in the absence of attacks of paroxysmal tachycardia. A syndrome of short P-R interval, normal QRS complex, and paroxysmal rapid heart action is described by Lown, Ganong, and Levine.[417] It occurs chiefly in females, the tachycardia in half the patients beginning after the fourth decade of life. Electrocardiographically the QRS complex, unlike its action in the Wolff-Parkinson-White syndrome, is devoid of slurring and does not exceed 0.08 seconds in duration. The evidence indicates that the mechanism underlying the syndrome is not one of anomalous AV conduction, as is believed to be the case in the Wolff-Parkinson-White syndrome, and the authors suggest that possibly stress with resultant hypothalamic discharge activating the adrenal glands and the sympathetic nervous system may sustain shortened AV conduction times, and, with period augmentation of stress, trigger outburts of tachycardia.

The clinical features of paroxysmal ventricular tachycardia have been presented by Armbrust and Levine,[418] who summarize their experience with 107 cases. Coronary artery disease was present in 75% of the cases, usually with recent or old myocardial infarction. Digitalis was considered responsible for precipitating a paroxysm in only a small number of instances. The immediate prognosis of an attack is very good, since in all but a few patients normal rhythm was resumed after appropriate therapy. The ultimate outlook in those having underlying heart disease was often grave, and even in the group of subjects in whom no organic heart disease could be demonstrated the threat of sudden death was present, as evidenced by one patient who died in a paroxysm and had a structurally normal heart at postmortem examination. The authors found quinidine the drug of choice, reserving intravenous administration for especially severe cases. Contrary to usual recommendations, Gilson and Schemm[419] report seemingly definite benefit from the use of digitalis in the presence of paroxysmal ventricular tachycardia in four cases. In three of these cases substantial additional doses of digitalis were superimposed on maintenance doses of digitalis which the patient had been receiving prior to the tachycardia, yet the tachycardia ceased with, or in spite of, these additional doses of the drug and heart failure was controlled in spite of the presence of the tachycardia. Symptoms which could have been interpreted as due to digitalis intoxication cleared with the improvement in cardiac function following the cessation of the tachycardia in spite of continued digitalis use. The authors conclude that the use of digitalis in ventricular tachycardia is not as harmful as the literature suggests and that support of the failing myocardium with digitalis may be an important aspect of treatment in prolonged ventricular tachycardia.

Of considerable recent interest has been the introduction and clinical application of procaine amide (Pronestyl) in the treatment of cardiac arrhythmias.† Although it is generally reasonably effective against ectopic beats and the supraventricular arrhythmias, the most important use of procaine amide has been shown to be in the control of ventricular tachycardias. Given orally, or in more severe cases intravenously, procaine amide abolishes most ventricular tachycardias and may succeed where quinidine has failed. The presence of large amounts of digitalis or quinidine in the body does not contraindicate the use of the amide. Hypotension is the most common serious toxic effect of procaine amide and is observed most frequently following intravenous use, but it may be seen after oral administration as well. As emphasized by Stearns and his collaborators,[422] the degree to which the blood pressure may fall is not related to control blood pressures nor to the type of arrhythmia present. Furthermore, blood pressure may fall in certain cases despite the use of distinctly slower procaine amide infusion rates than are used in most cases or in response to total doses averaging less than 500 mg. Repeated blood pressure determinations are therefore more important than the electrocardiogram as a guide to the safe administration of procaine amide. Besides coronary insufficiency and convulsive seizures secondary to hypotension, psychoses or severe mental depression have developed in a few patients, and in two asthmatic patients severe attacks developed on exposure to the amide.[423] Ventricular tachycardia induced by the procaine amide itself when administered for other arrhythmias may be an occasional complication.[424] Chills and fever following oral use of the drug have

† References 420 and 421.

been recorded by Leibowitz,[425] and Inouye and others[426] report a severe case of agranulocytosis occurring during maintenance dosage of procaine amide.

In studying ventricular standstill and fibrillation produced experimentally 205 times in 72 dogs, Kay[427] found that adequate cardiac massage was one of the most important steps in treating either of these potentially fatal complications. The injection of procaine, even when accompanied by cardiac massage, proved unsatisfactory in the treatment of ventricular fibrillation, but in 189 experiments wherein cardiac massage for one or two minutes was associated with electrical defibrillation successful control of the ventricular fibrilation was achieved in every instance. In 29 other animals, in whom the heart was allowed to fibrillate for periods varying from 3 to 62 minutes, the heart was massaged during the entire time, and after electrical defibrillation at the end of the allotted time all of the animals recovered without evidence of neurological changes. The upper limit for cardiac asystole owing to either cardiac arrest or ventricular fibrillation is three to three and one half minutes before serious and shortly irreparable damage to the central nervous system ensues.[428] When rhythmic cardiac massage is attempted to support the circulation while awaiting the beneficient effects of pharmacological agents or electrical stimulation in the correction of the arrest or ventricular fibrillation, the heart should be compressed at least 60 times a minute to achieve the most efficient blood flow.[429] Cole[430] describes a case in which cardiac arrest occurred during spinal anesthesia with institution of cardiac massage within 5 minutes and with asystole lasting a total of 11 minutes. Cerebral (and pulmonary) edema followed, with coma, convulsions, cyanosis, hyperpyrexia, tachypnea, tachycardia, and insensitivity to light. Earlier, Seldon and his co-workers[431] had reasoned that permanent brain damage following acute cerebral anoxia resulted not solely from the duration of the anoxia itself but also from the duration and severity of the period of postanoxic cerebral edema. With this in mind, Cole during the 24-hour period following the accident gave three injections of 100 cc. of human serum albumin containing a total of 75 gm. of albumin and in the course of the next three weeks observed a gradual progression to total recovery.

The cardioinhibitory carotid sinus syndrome, with its sudden episodes of dizziness, faintness, syncope, or convulsions resulting from temporary cardiac arrest, has been well summarized by Draper[432] and by Evans.[433] The syndrome is predominantly a disease of older men, but it should be considered in all patients manifesting the symptoms just mentioned. Although functional states such as anxiety, worry, or fatigue frequently aggravate symptoms, organic disease such as coronary or cerebrovascular disease is usually present and prognosis usually depends upon the disease itself. As demonstrated by Rudnikoff,[434] insulin may also increase the effects resulting from carotid sinus stimulation, a factor to be borne in mind whenever diabetics are brought to surgery or evince subjective symptoms suggestive of the carotid sinus syndrome.

IX. CONGESTIVE HEART FAILURE

The complexities of the fundamental and contributory mechanisms leading to the clinical syndrome of congestive heart failure continue to defy full understanding. Nonetheless, distinct advances have been made in this field. In comparison with the immediately preceding period, the most striking advance of the last three years has been the subsidence of contention between the proponents of a primary cardiac

basis for congestive failure, backward failure, and the supporters of a primary renal basis, forward failure. Most observers have now reached a broad middle ground whereon they take the position that one or the other of these principal mechanisms is preponderant while conceding that the other makes an important secondary contribution to the fully developed clinical picture.[435] A practical demonstration of the two distinct types of cardiac failure is afforded by the patient of Newman and Fishel [436] with hypertensive and arteriosclerotic heart disease in whom cardiac failure was precipitated either by administration of salt or by cessation of digitalis therapy. With salt administration there was a marked rise in both weight and venous pressure but no dyspnea; mercurial diuretics then lowered both weight and venous pressure simultaneously. When digitalis was withheld, on the other hand, there was a comparable rise in venous pressure but no rise in weight and dyspnea and orthopnea became prominent; this failure could not be controlled by increasing the dosage and frequency of mercurial injections. The first type of failure was ascribed to the gradual retention and equal distribution of salt and water throughout the extracellular space. The failure following digitalis withdrawal was considered more acute and due to brief periods of discrepancy between the outputs of the two ventricles with subsequent redistribution of fluid on the venous side.

Certain flaws in both the forward and backward theories of cardiac failure, too detailed for summary here, have led Little [437] to postulate that under the stimulus of decreased mixed venous partial pressure of oxygen, due either to increased oxygen utilization or to inadequate blood oxygen capacity, the cardiac output increases and the venous capacity decreases owing to active venoconstriction. Little suggests that these changes are mediated by reflexes or humoral mechanisms of unknown character but presumed to be analagous to those acting on the arterial side through stimulation of the chemoreceptors in the carotid body and the aortic arch. Under these circumstances, if the response of the heart is inadequate, as in acute congestive or anemic heart failure, the net effect on venous or atrial pressure would be a marked increase owing to the fact that venoconstriction would be unimpaired. As the author points out, this concept does not imply that a decrease in mixed venous partial pressure of oxygen by itself, with consequent venoconstriction, as in cyanotic pulmonary disease or cyanotic congenital heart disease, would necessarily result in an elevation of venous or atrial pressure. In these and other instances of inadequate oxygenation congestive failure would not appear so long as the heart retained its capacity to increase its output in proportion to the decrease in venous capacity resulting from decreased oxygen tension. Observations possibly in support of this theory are those of Viar and his associates,[438] who have found that the change from a sitting to a recumbent posture produces a well-marked increase in urinary sodium and chloride excretion. Compression of the neck of the sitting subjects causes increased output of sodium and chloride, but this has little or no effect in recumbent subjects. Cardiac output varied in the same direction as sodium excretion when posture was changed but showed no measurable change following compression of the neck in sitting subjects. The authors therefore suggest that there is a central mechanism which functions as a "volume center," tending to maintain homeostasis by increased tubular reabsorption of sodium when conditions occur which reduce the volume of intracranial extracellular fluid. No support was found for the concept that decline of cardiac output is of importance in relation to sodium retention.

In support of the position that renal dysfunction is responsible for the clinical phenomenon of heart failure when the primary disease is in the heart, Friedberg [439] cites four cases of nephrosis secondary to carbon tetrachloride inhalation, in each of which the clinical picture of congestive heart failure, including pulmonary edema, developed. As in patients with classic heart failure, in these persons with lower nephron nephrosis the syndrome of congestive failure developed on intakes of sodium and water which were quantitatively in the range tolerated by normal persons without the development of symptoms. Yet each of the four patients was considered to be without clinical evidence of heart disease. Sodium and chloride and water balance studies on 50 patients of whom 39 suffered from congestive circulatory failure of cardiac origin have led Schroeder [440] similarly to conclude that, although initiated by the heart, congestive circulatory failure is mediated principally through the kidney. Disturbances of both salt and water balances may be present and may result from hormonal effects upon renal regulatory mechanisms. A balanced view of the renal factor in congestive heart failure has been presented by Stead,[441] with the conclusion that the treatment of edema of congestive heart failure can be divided into two phases. First, measures should be taken to make the circulation adequate to body needs, increasing cardiac output by the administration of digitalis, decreasing body weight and activity, and correcting disease states which either increase heart load or decrease myocardial efficiency. When these measures are effective, edema will not develop on a normal diet. If these measures prove inadequate to restore cardiac compensation and prevent edema, however, attention is then directed toward restricting sodium chloride in the diet, sometimes severely, increasing excretion of sodium chloride by the use of mercurial diuretics and anion exchange resins, and directly removing fluid from the body by paracentesis or subcutaneous drainage.

Antidiuretic action of the urine of patients in cardiac failure has been observed by Bercu and his co-workers,[442] but it has not been possible to identify the effective substance as a posterior pituitary principle nor to clarify the role of this substance in the development of cardiac failure. Studying the effects of vasopressor (Pitressin) injection in normal subjects, Holland and Stead [443] could demonstrate no effect on the excretion of sodium, chloride, and potassium in persons receiving hypertonic and isotonic sodium chloride solutions and have concluded that neither vasopressin nor endogenously produced antidiuretic hormone will produce the picture of sodium retention seen in congestive heart failure. With regard to the possible role of adrenocortical hormone in sodium retention in congestive failure, Goldzieher [444] has marshalled evidence to show that there is increased cortical secretion if the supply of oxygen is reduced or the body's demand for oxygen is increased. That this evidence is not applicable to congestive heart failure, however, seems obvious from the work of Lasché and his associates [445] in the evaluation of adrenal cortex function in 23 patients with various degrees of failure. When the onset of failure is recent the rates of steroid hormone excretion may be normal, but in the majority of cases a significant lowering is observed. Hypoglycemic unresponsiveness following insulin administration appeared in patients with decompensation of more than six months' duration. Mercurial diuretics raised the excretion rate of 11-oxysteroids tenfold in edematous patients but produced little change in the urinary levels in the nonedematous patients, and they did not increase the urinary 17-ketosteroid excretion. The authors accordingly conclude that there is decreased adrenocortical function in chronic cardiac decompensation and that there may be retention of 11-oxysteroids at the renal level

in such patients. In any event, however, as pointed out by Newman,[446] the ultimate responsibility for sodium retention rests with the specific selective mechanisms of the renal tubular cells, whose reabsorptive activity must be sensitive to factors other than the reduction in the amount of fluid presented to them by the inadequate circulation. The effects on tubular cells of posture, exercise, humoral substances, and the renal nerves remain to be clearly determined, as does the nature of the profound metabolic effects of insufficient cardiac output on peripheral tissues other than the kidney.

Some insight of the nature and possibly highly significant role of these peripheral metabolic effects in the development of congestive failure is provided by the detailed study by Iseri, Boyle, and Myers [447] of water and electrolyte balance during recovery of seven patients from severe congestive failure on a 50 mg. sodium diet. Inferring that movements of water and electrolytes during the development of congestive failure were opposite to those which they observed during recovery, these authors suggest that during the onset of congestive failure the extracellular compartment expands by the retention of water containing sodium in physiological or hypertonic proportions, potassium in isotonic concentrations, and chloride in physiological or hypotonic proportions. At the same time, the intracellular compartment increases in volume but loses significant quantities of sodium, potassium, and probably nitrogen. The shifts of water and electrolytes between the two compartments are probably not secondary to changes in extracellular acid-base equilibrium, since sodium and potassium move in parallel rather than in opposite directions. The demonstration of elevated plasma sodium concentrations during failure in four of the seven patients is inconsistent with the possibility that cardiac edema represents a primary water retention and that shift of sodium and potassium out of the cells is an osmotic compensation for dilution. The findings of the study support the hypothesis that congestive failure is accompanied by an alteration of cellular metabolism manifested by the liberation of ionized base from osmotically inactive constituents of the protoplasm. This change then tends to make intracellular fluid hypertonic in respect to interstitial fluid, thus accounting for the cellular uptake of water and release of sodium and potassium that is apparently associated with the development of congestive failure. Somewhat parallel studies by Elkinton and Squires and their associates ‡ confirm this observation that during recovery from congestive failure water is lost from cells and potassium taken up, and these observers likewise advance the hypothesis of changes in intracellular osmolarity secondary to changes in size and degree of dissociation of various potassium phosphate and proteinate molecules which take place during processes of cellular metabolism. The prospects for a broad advance along these lines toward a more fundamental understanding of congestive failure seems most promising.

The need for greater understanding of cardiac metabolism at the cellular level as well is emphasized by the case of cardiac failure in a "normal" heart reported by Noehren and McKee.[452] Having enjoyed excellent health prior to the age of 51, this patient then developed intermittent signs and symptoms of cardiac insufficiency and finally died six years later in decompensation. At postmortem examination, however, the heart was anatomically normal. In the absence of an anatomic diagnosis, the authors discuss the possibility that the case provides an example of cardiac failure caused by inadequate musculature per se. Clinically, circulatory

‡ References 448, 449, 450, and 451.

decompensation due to limited muscle strength is well recognized, being seen with overvigorous intravenous fluid administration or following the suddenly-imposed burden created by rupture of a valve leaflet. Again, in deficiency states there may be no anatomical heart change, and a decompensation is overcome by physiologic means, such as the administration of thiamine chloride. Extending their reasoning to cases shown at autopsy to have moderate degrees of coronary atherosclerosis, the authors suggest that these anatomical findings do not necessarily prove that the vessels were incompetent and the cause of the heart failure. The fact that such coronary disease had undoubtedly been present for years and equally certainly could not have been changed in any way by the digitalis, which nevertheless could reverse cardiac failure and permit long periods of compensation, suggests that change in the musculature itself may control the timing of heart failure in some cases. It seems highly probable that an as yet obscure process of muscular aging may underlie heart failure in many older patients and that what may be merely coincidental anatomic findings should not form the sole basis for the diagnosis of a physiologic phenomenon. Noting the similarity between what happens in the heart-lung preparation in the course of some six hours in the absence of any known injurious influences and what happens in man in the course of some six decades, Harrison points out that in both instances all known variables may remain constant except time, yet with the passage of this time the myocardium may become exhausted by a process of aging unassociated with increased load or coronary sclerosis. Regardless of the cause of the failure, from coronary catheterization studies Bing and Daley § have concluded that in the failing heart the coronary unit blood flow is normal and the coronary arteriovenous difference slightly increased but that the cardiac output is low. With these findings the conclusion is reached that the essential disability of the failing human heart is a reduction in its ability to transfer oxidative energy into useful work, that is, the failure of mechanical efficiency.

In this connection the detailed review by Olson and Schwartz [455] of recent researches in myocardial metabolism in both the normal heart and in congestive heart failure is of great interest. After discussion of the oxidation-reduction and coenzyme systems involved and consideration of the muscular contraction and release of energy caused by depolymerization and shortening of actomyosin fibrils of the myocardium, the authors group the cases of clinical heart failure into two main types. In one there are disturbances in energy production attendant upon oxygen lack, as in anoxia and anemia; enzyme or coenzyme lack, as in beriberi, or hormonal lack or imbalance, as with thyrotoxicosis. In the second group are disturbances of energy utilization, as indicated by studies such as those of Bing and Daley cited above on patients with congestive failure due to hypertension or valvular disease in whom coronary blood flow, oxygen extraction, and substrate utilization are not impaired. In the former, or high-output failure group, in which oxidative metabolism or phosphate bond conservation is impaired, digitalis administration leads to little or no clinical benefit. In the second group, however, digitalis generally produces marked clinical improvement, suggesting that the primary action of digitalis may be to increase the ability of the actomyosin fibril to utilize available phosphate bond energy and thereby increase cardiac work without com-

§ References 453 and 454.

parable increase in oxygen consumption. That digitalis glycosides may also have some effect on energy production in myocardial tissue is evidenced by the studies of Wollenberger,[456] who added ouabain and C^{14}-labeled glucose simultaneously to slices of dog myocardium. Analysis showed that the rate of glucose oxidation was doubled although there was no increase in glucose uptake. Lactic acid production, on the other hand, was greatly reduced by ouabain. The author suggests that in cardiac muscle the glycosides accelerate the formation of pyruvate from glucose and lactate, but he believes it unlikely that the stimulation of cardiac energy metabolism by these compounds is the cause of the increase in the force of contraction. The functional and metabolic changes both are more likely the product of a cellular alteration which remains obscure.

The concept that the reduction in heart muscle potassium in congestive heart failure is the result of heart muscle edema has been refuted by Clarke and Mosher,[457] who failed to find any real difference in average heart water content between normal and diseased hearts, although the potassium content in the latter showed a definite decrease. Similarly, the potassium content of heart muscle in digitalized cardiac patients is higher that that of undigitalized patients, with no or only slight changes in the water content. The authors conclude that digitalis glycosides exert a direct chemical action on heart muscle, tending in congestive heart failure to restore the alkali metal values and ratios of heart muscle to near normal levels. Clinical observations bearing on this point are described by Harvey and his associates,[458] who studied the effects of digoxin by cardiac catheterization in five patients with left-sided heart failure. A significant rise in cardiac output and stroke volume, accompanied by a decrease in pulmonary arterial pressure, was observed in each of the five patients. The fact that these changes took place without alteration in the right ventricle and diastolic pressure points to a direct action of digoxin upon the myocardium rather than on the systemic venous system, as proposed by McMichael in the period just prior to that covered by this review.

Interest in the purified cardiac glycosides continues. Parsonnet, Bernstein, and their fellow workers[459] report on the use of a pure combination of Digitalis lanata glycosides (digilanid), which they find to be stable, uniform in composition, and fulfilling all the usual criteria for an acceptable digitalis preparation, with the advantage over digitoxin of being rapidly excreted should toxic effects develop. Amorphous gitalin has been studied by Batterman, DeGraff, and Rose[460] and found to possess a greater therapeutic range than any available digitalis preparation or purified glycosides. The authors state that amorphous gitalin permits slow or rapid digitalization with a greater degree of safety than was heretofore possible, using a dose smaller in terms of the toxic dose than that possible with other purified digitalis preparations. Because of its greater therapeutic range, amorphous gitalin without the occurrence of toxicity may permit improvement in cardiac efficiency in patients refractory to digitalis and the other purified glycosides. The authors conclude therefore that amorphous gitalin is the digitalis preparation of choice for the treatment of the usual patient with congestive heart failure.

Despite, or perhaps because of, the several digitalis preparations available, problems in digitalis toxicity still arise to plague the clinician. That digitoxin toxicity may not be accompanied by yellow vision and that with digitoxin toxic

signs frequently appear before symptoms, necessitating close clinical supervision of the patient, have been reemphasized by Moody.[461] Fifteen patients presenting 16 episodes of increasing congestive heart failure as a manifestation of digitalis toxicity have been reported by Batterman and Gutner.[462] The basis for the syndrome of congestive failure as a toxic sign is considered by the authors to be the result of a direct muscular action of the excess glycoside, with a consequent decrease in myocardial efficiency. Although none of the patients in this report presented congestive failure as the only indication of digitalis toxicity, there was no correlation between the severity of the classic toxic signs and the advent of impaired myocardial efficiency. It is therefore conceivable, on a purely pharmacologic basis, that in some patients this digitalis effect upon contractility might be the predominant action and that congestive heart failure might occur in the absence of other well-accepted evidences of digitalis toxicity. The authors conclude that in any case of severe congestive failure in which the history suggests that a toxic dose of some digitalis preparation may have been taken, the sensible program is to discontinue digitalis and to evaluate the patient further on bed rest alone before instituting any other therapeutic measure. Delirium as another unusual toxic effect of digitalis has been reported in six cases by King.[463] In each case the disturbance disappeared entirely upon withdrawal of the drug or reduction in its dosage. The delirium seems to be due to drug intoxication rather than to changes in circulation or absorption of edema products, and causative preparations included digitalis, lanatoside C, and digitoxin.

The interrelation between potassium metabolism and digitalis toxicity in heart failure has been well illustrated by the patients described by Lown and his collaborators.[464] In a series of 10 patients with congestive heart failure potassium depletion, either occurring spontaneously with malnutrition and gastrointestinal disorders or induced by mercurial diuresis after pretreatment with ammonium chloride, was found to be associated with increased sensitivity to digitalis. Decreased tolerance to digitalis following desoxycorticosterone acetate therapy in two patients was also observed. In one digitalized patient digitalis toxicity was precipitated by the intravenous injection of insulin and glucose, following which hypopotassemia developed. Increased myocardial sensitivity to digitalis observed after potassium losses seems probably to be the result of alterations in the intracellular potassium distribution, because no significant changes in serum or extracellular potassium were observed in 8 of 10 patients. Further studies by Lown and his associates,[465] using acetyl strophanthidin and the artificial kidney on dogs, have shown that a marked decrease of the dose of the glycoside is necessary to produce toxicity when serum potassium is distinctly lowered, and, conversely, a marked increase in the dose of strophanthidin is required for toxicity when the potassium serum level is increased. A relationship between thyroid hormone and digitalis toxicity has also been demonstrated by Deering, Barnes, and Essex.[466] Toxic doses of digitalis given to animals with mild or moderate hyperthyroidism caused extensive degenerative changes in the myocardium of animals surviving more than five days or resulted in death in one or two days in animals in which microscopic changes were not found. Studies of digitalis or thyroid extract toxicity alone failed to induce myocardial lesions of comparable severity or frequency. A final point of interest with regard to digitalis is the demonstration

by Sutton [467] and by Cathcart and Blood [468] in normal subjects and in patients in congestive heart failure that digitalis in usual or toxic doses produced no effect on either the clotting or prothrombin times of the persons observed.

Perhaps the best introduction to a brief survey of the present state of the mercurial diuretics in the treatment of congestive heart failure is provided by an excellent short review by Batterman [469] on this subject. The clinical effectiveness and relative safety of the mercurial diuretics have led many to recommend their unrestricted use and to advocate drastic methods for dehydration as a routine procedure. As a consequence there have been described an unusual number of clinical syndromes related to excessive diuresis, and cases falling under these several headings far exceed in numbers those reactions related to mercurialism or idiosyncrasy to the injected agents. With these points in mind, Batterman points out that of 1,000 patients with symptoms with cardiac decompensation probably 900 or more can be improved and often maintained for prolonged periods on no further treatment than physical rest and adequate digitalization. In the remaining 10% of patients the mercurial agents properly administered will remove the edema in approximately 90%. In other words, only 1% of the patients with edema will ultimately require sodium restriction by either dietary regulation or resin control. Yet, because these are exactly the patients who appear in teaching centers the lessons learned from their care tend to be applied indiscriminately to the great mass of patients with milder instances of failure, who need no such strenuous measures and, indeed, who may suffer discomfort and even danger therefrom.

Of recent interest has been the clinical evaluation and widespread acceptance of a new mercurial diuretic, mercaptomerin sodium (Thiomerin sodium). Pharmacologically this substance has been declared much the least toxic of the presently available mercurial agents, and clinically upon subcutaneous administration it evokes little or no local irritation yet induces a degree of diuresis similar to that obtained with intravenous administration of meralluride (Mercuhydrin). Extensive clinical studies of || subdermal injection of both meralluride and mercaptomerin, the latter agent in one series of patients being self-administered in a manner analagous to the use of insulin by diabetics, have demonstrated that subcutaneous administration of these compounds is well tolerated and equally as effective as intravenous injection in about 75% of the patients involved. Troublesome reactions in about a quarter of the patients include pain, ecchymosis, fibrous nodules, or combinations thereof with intensity sufficient to arouse patient protest. New and less irritating mercurial diuretic preparations for oral administration are currently coming into clinical use and if initial favorable reports ¶ are substantiated may well supplant the injectable material for maintenance care in most patients in whom mercurial therapy is indicated. A conservative note is sounded here, however, by Overman and his associates,[475] who have concluded, from tracer studies of the urinary excretion of radioactive mercury following oral administration of a mercurial diuretic, that poor absorption, low blood concentration, and low urinary excretion of mercury following oral administration cast doubts on the usefulness of this compound in the treatment of chronic congestive heart failure.

|| References 470, 471, and 472.

¶ References 473 and 474.

In a group of edematous patients who were excreting negligible amounts of dietary sodium in the urine, Lesser and others [476] found that following mercurial diuresis there was invariably an appreciable loss of potassium, to which might be attributed such clinical symptoms as weakness, nausea, and ventricular premature contractions. In these patients the chloride and water loss attendant upon diuresis led to a relative alkalosis, with a loss of intracellular potassium and intracellular sodium. In detailed metabolic studies on the effect of meralluride on body water and electrolytes in 10 patients with congestive heart failure, Schwartz and Wallace [477] showed that the patients were responsive to the diuretic agent until approximately normal weight was reached. At this point, in most of the patients there was a fall in serum chloride and a rise in bicarbonate, often with a negative potassium balance and a fall in serum potassium concentration. In seven of eight patients these findings coincided with the appearance of mercurial unresponsiveness. When ammonium chloride was administered in amounts sufficient to return serum chloride and bicarbonate normals to value, mercurial responsiveness was restored. Overadministration of ammonium chloride with mercurial diuretics, on the other hand, as demonstrated by Bergner and others,[478] leads to varying degrees of acidosis, with high chloride levels, reduced carbon-dioxide-combining power and serum pH, and in some instances lowering of the sodium level. Under these circumstances serum potassium tended to be increased. Correction of the acidosis by temporary withdrawal of the ammonium chloride restores electrolyte values to normal levels. The intermittent use of ammonium chloride prevents severe acidosis but allows for the usual favorable combined effect with mercurial injections.

The low-sodium syndrome resulting from excessive diuresis is well recognized and need not be expanded upon here.[479] Equally serious is the occasional sensitivity reaction to mercurial diuretics, which may be noted on parenteral administration of any of the several agents available. As emphasized by Wallner and Herman,[480] severe and even fatal reactions may be foreshadowed by temperature elevations and appearance of rash and by subjective complaints such as retrobulbar pain, weakness, and dizziness following injections prior to the one precipitating the full-blown reaction. Clinical alertness to such findings in the patient receiving repeated mercurial administrations may well forestall a catastrophe. As in the case of Reeves,[481] it is usually possible, when symptoms and signs of hypersensitivity appear, to substitute some other mercurial diuretic for continued administration. Acute dehydration, with sudden peripheral vascular collapse, bradycardia, shaking chill, and temperature rise, after copious diuresis, with subsequent rapid recovery, has been described by Rechtschaffen and Gittler.[482] Single cases of neutropenia in patients following use of mercurials have been reported by Silverman and Worthen [483] and by Bender and others.[484] In the second case the striking improvement noted in both the peripheral blood and the bone marrow following the use of dimercaprol (BAL), seemingly too rapid for spontaneous remission, suggests that the dimercaprol may have had a beneficial effect.

Interest probably out of proportion to their ultimate usefulness has accompanied the introduction and clinical evaluation of the several cation exchange resins for control of congestive heart failure and other edematous conditions. The details of chemical and physiologic backgrounds may well be left to the excellent reviews #

References 485, 486, and 487.

which have appeared. In general, it may be said that the hydrogen and ammonium exchange resins have been found too prone to induce acidosis and potassium depletion and have been largely supplanted by exchange resins in the potassium series. Potassium exchange resin provides base, which can prevent both acidosis and potassium depletion but by the same token does not take up sodium as efficiently and in some circumstances may contribute toward hyperpotassemia. With all cation exchangers there is an increasing tendency toward nausea and other gastrointestinal symptoms as the dose is increased. Diminished renal function from any cause, where acidosis or hyperpotassemia may already be a factor, generally contraindicates the use of exchange resins. An exception may be the use of an ammonium exchange resin to attempt to control hyperpotassemia secondary to renal disease when the artificial kidney is not available. As demonstrated by Elkinton and his collaborators [488] this method is clinically feasible and the tendency to accentuate acidosis by concurrent sodium removal is controlled by administration of sodium bicarbonate.

In the control of edema, doses of cation exchange resins in the neighborhood of 45 gm. per day may remove about 2 gm. of dietary sodium.[489] As emphasized by Danowski and others,[490] however, this removal is quite insufficient to permit unlimited intake of dietary sodium, and the much-heralded promise that the exchange resins would allow the harrassed cardiac to resume his normal dietary habits is proving a false hope indeed. There has developed general agreement * that the principal sphere of value for the use of cation exchange resigns in the control of congestive cardiac failure lies with those patients refractory to ordinary mercurial and dietary regimens. In these patients prolonged resin administration may successfully reduce or eliminate an otherwise unmanageable edema, but to the ordinary cardiac patient the resins offer little if any advantage.

Before passing from sodium control, it is of interest to note Talbott's [495] review of the use of lithium salts as a substitute for sodium chloride. Because of widely publicized fatalities, the lithium salts have been completely dropped from the therapeutic program, despite the fact that they appear to provide the only really satisfactory taste equivalent of ordinary salt. Administering lithium carbonate tablets in quantities equivalent to 2.2 to 4.6 gm. lithium chloride daily for as long as 19 days, Talbott found that in only a fraction of the patients did serum lithium concentrations reaching a level of 0.7 to 1.0 mEq. per liter develop, at which point the symptoms of gastrointestinal irritability, anorexia, drowsiness, depression, and tremors appear. Inasmuch as the amounts of lithium necessary to flavor food fall below those used in these studies, it might well be possible to restore lithium salts to clinical usefulness, providing that there is sufficient bedside and laboratory alertness to catch the occasional patient in whom the cumulative effect of small doses may lead to toxic symptoms.

The usefulness of anticoagulant therapy in patients with congestive failure has been established by several well-studied series.† As pointed out by Marvel and Shullenberger,[498] rapid and marked diuresis plays an important role in the pathogenesis of thromboembolic complications encountered in patients being treated for congestive heart failure, by producing hemoconcentration and increasing blood viscosity and at times seemingly favoring increased prothrombin values,

* References 491, 492, 493, and 494.

† References 496, 497, 498, and 499.

elevated fibrinogen values, rapid coagulation times, and increased globulin fractions. Between the sixth and ninth days of therapy, at which time the average hematocrit value for all patients is at its peak and during which time a concentration of factors favoring intravascular thrombosis is present, is the commonest period for thromboembolic complications. As stressed by Stats and Davison,[500] cardiac patients with moderate to severe failure require smaller doses of bishydroxycoumarin (Dicumarol) to produce the desired hypoprothrobinemic effect.

A seemingly valuable, albeit Spartan, maneuver for the relief of the occasional patient with refractory congestive failure is ligation of the inferior vena cava, originated and clinically studied rather extensively by Cossio and Perianes.[501] Significant and even surprising improvement in a significant number of patients in their total series of 90 patients operated upon indicates that a substantial proportion of patients undergoing the ligation may derive benefit for months and even years if adequate medical therapy is maintained postoperatively. The patients most benefitted were those with congestive failure secondary to hypertension or rheumatic heart disease, especially when there had been symptoms prior to operation suggesting phlebothrombosis or pulmonary infarction. The improvement therefore was ascribed not only to the hemodynamic changes, with pooling of blood in the lower extremities even in recumbency, but also to the possible elimination of a source of minute emboli which may be factors in intractable heart failure. Similar results have been reported by Donzelot and his associates,[503] with definite improvement in 33 out of 50 patients with chronic congestive heart failure following inferior cava ligation.

In the treatment of acute pulmonary edema Luisada [504] has shown that the antifoaming effect of alcohol vapor by inhalation affords prompt relief in more than half of cases and some distinct improvement in the greater part of the remainder. Gootnick and his co-authors [505] report similar findings. The alcohol presumably alters the surface tension at the fluid-air interface, thereby collapsing the foam bubbles. The volatility of the alcohol permits penetration of the treatment into the finer air spaces. In a number of especially severe cases alcohol vapor brought relief to a patient who obtained no benefit from previously administered accepted treatments for pulmonary edema such as drugs, venesection, oxygen, and positive pressure respiration.

The problem of apparently or truly refractory congestive heart failure is too complicated and extensive for consideration here, but reference may be made in closing to the excellent papers on this subject by Soloff,[506] Proger and O'Connor,[507] and Friedberg and Halpern.[508]

X. PERIPHERAL VASCULAR DISEASE

Additional experience with penicillin in the treatment of cardiovascular syphilis seems further to establish this antibiotic as the drug of choice in the treatment of all phases of the disease. Reporting on a series of 111 patients, Stokes and others [509] have found little evidence that significant therapeutic shock (Jarisch-Herxheimer reaction) occurs in a full dose use of crystalline penicillin G on a two-hour round-the-clock schedule of 50,000 to 100,000 units per injection, for a total of 5,000,000 to 10,000,000 units, even without the conventional heavy metal "preparation." Penicillin has none of the vasculotoxic effects so troublesome with the arsenicals, and to date no unequivocal instances of therapeutic paradox (worsening of the

patient because of rapid scarring in the healing process) have been noted, even in patients so badly damaged that it might have been expected. Penicillin is admirably tolerated by the decompensated heart, with clinical improvement in a high proportion of cases, and the anginal pain of cardiovascular syphilis is relieved without recognizable shock or paradox in most instances. One-third to one-half of persons with various forms of syphilitic aortitis showed distinct improvement, although, of course, no change in large saccular aneurysms could reasonably be expected. Blood serological results of penicillin treatment are not impressive, as might be anticipated from experience with other types of late syphilis, but can be ignored when adequate dosage schedules are known to have been received by the given patient. Bruetsch [510] and Sinclaire and Webster [511] are in agreement that the Jarisch-Herxheimer reaction is of no great significance in penicillin therapy of cardiovascular syphilis. Miller and Bernstein,[512] however, cite a case with clinical and electrocardiographic evidence of acute coronary insufficiency following the injection of 600,000 units of penicillin procaine in a 48-year-old Negro woman with uncomplicated syphilitic aortitis. The authors considered this a Jarisch-Herxheimer reaction, but they continued treatment without recurrence of precordial pressure and an electrocardiogram taken within five weeks had returned to normal. Kampmeier and Morgan,[513] on the other hand, consider the Jarisch-Herxheimer reaction of sufficient significance to recommend "preparing" the patient with cardiovascular syphilis for intensive penicillin treatment by several weeks of bismuth and iodide therapy or several days of markedly reduced penicillin dosage. These workers add that bismuth and iodide are probably of some value in their own right as well in the treatment of chronic syphilis. An interesting case of a saccular aortic aneurysm in a 31-year-old white man with a persistently negative serologic test for syphilis, no history of infection, and no other evidence of syphilis has been described by Kahn and Kilbury.[514] At postmortem examination the aortic lesions showed extensive medial scarring and destruction of elastic tissue typical of syphilitic aortitis, with no evidence of rheumatic aortitis.

For the treatment of syphilitic aneurysms of the arch of the aorta Linton and Hardy [515] suggest a "pack" method of intrasaccular wiring by means of which from 100 to 500 feet of stainless steel wire are inserted, with resultant thrombosis and arrest and even prevention of further aneurysmal dilatation. In a series of 18 patients treated in this manner the authors observed that, while the treatment is not ideal, relief of symptoms is effected in the majority and a prolongation of life in a gratifying number. For the more accessible aneurysms of the descending thoracic aorta extensive experimental studies have been reported, involving resection of the defects and replacement with venous or pericardial autogenous grafts, sometimes reinforced with fascia from the thigh, or by preserved venous homografts.‡ Lam and Aram [519] describe the case of a patient with an aneurysm of the descending aorta about the size of a large grapefruit, which was treated by the use of a homograft removed from a cadaver 10 hours after death. The aneurysmal sac was not removed. Unfortunately the patient died about three months after the operation owing to a large mediastinal abscess in the region of the old aneurysm, but histological examination of the aorta showed healing of the graft adequate to prevent hemorrhage. It seems likely that this technique will prove feasible.

‡ References 516, 517, and 518.

For the safe production of controlled clotting for progressive endoarterial occlusion of aneurysms of the aorta arising distal to the renal arteries. Blakemore [520] recommends the method of electrothermic wiring. When sufficient wire is introduced into the aneurysmal sac and heated to an average temperature of 80 C. the wire in the aneurysm becomes sufficiently hot to cause a deposit of clot-stimulating protein coagulum. Such wire as may protrude into the fast-moving blood current of the aorta is cooled so rapidly that it remains uncoated and therefore fails to stimulate clotting where none is wanted. A useful adjunct to this method is partial occlusion of the abdominal aorta proximal to the aneurysm using polythene-dicetyl phosphate film. Aneurysm of the splenic artery should be considered when there is severe intra-abdominal bleeding in the absence of trauma, cancer, or a source of hemorrhage in the female pelvis and also when a mass of obscure origin is found in the upper abdomen. An expansile pulsation, if a mass is present, or the presence of a bruit heard over the left side of the abdomen or the lower ribs posteriorly facilitates diagnosis. According to Palmer,[521] splenic artery aneurysms should be removed, because of the likelihood of rupture, a usually fatal complication.

Thorough discussions of translumbar aortography have been offered by Smith, Rush, and Evans [522] and by Leriche and his assistants,[523] the latter group providing a series of striking x-ray illustrations of the information which may be derived from this procedure. Although of limited diagnostic application, translumbar aortography greatly aids in the localization of traumatic or congenital pelvic aneurysms prior to surgery. In obstructive peripheral vascular disease the diagnosis is usually made clinically but aortography may provide information on the exact location and extent of the lesion which may be invaluable if reconstructive surgery, including grafting, is being considered. If the obliteration is in the external iliac artery the prognosis is more grave, since the common iliac has no collateral branches; in this event whenever possible the obliteration should be removed and a vascular graft inserted. In cases of femoral occlusion it is the refilling of the popliteal artery below the obstruction that determines the future of the patient. The deep femoral artery is seldom involved, and it is through this vessel that the collateral circulation to the popliteal develops. If the popliteal artery is not refilled, the patient will eventually come to a midthigh amputation. The unusual but not excessively rare thrombotic occlusion of the lower aorta can be well confirmed by aortography.§ When the proximal end of the thrombus can be shown to lie sufficiently below the renal arteries to permit surgical manipulation to these vessels, the patient should have a resection of the segment of the aorta containing the thrombotic process, not only as an additional means beyond sympathectomy of interrupting the sympathetic outflow to the lower extremity but also to prevent the proximal continuation of thrombus formation to the point of occluding the renal arteries.

Of the factors influencing the development of cerebrovascular accidents Wilson and his associates [526] found in a series of clinical and pathological studies on 542 cases that there was evidence of cardiocirculatory insufficiency of some sort in 451, or 83%, of the total group. On the basis of this finding the authors conclude that circulatory inadequacy plays an important part in the etiology of cerebrovascular accidents and that preventive measures and treatment should be directed toward maintaining the general circulatory status at an optimum level. Bean and

§ References 524 and 525.

his group [527] emphasize that some instances of hemiplegia, convulsions, coma, and other extreme neurological symptoms coming on in association with myocardial infarction may be secondary entirely to insufficient cerebral blood flow resulting from inadequacy of systemic blood flow, without any thrombosis or embolization of arteries supplying the affected parts of the brain. In these circumstances vigorous therapy designed to restore adequate blood pressure and cerebral circulation may be accompanied by dramatic improvement and even disappearance of cerebral symptoms. This group of patients accordingly comprises a particularly favorable type of cerebrovascular "accident," and special efforts should be made to recognize the occasional association of such accidents with systemic vascular catastrophe. Support of this position from the laboratory point of view is provided by the observations of Scheinberg,[528] who found that mean cerebral blood flow in 14 subjects with heart failure was 39% less than the mean for normal young subjects. Cerebral vascular resistance at the same time was increased 100% over normal, a finding compatible with the assumption that the increase in resistance of the cerebral vessels results from vasoconstriction, the mechanism of which is not clear.

On the assumption that cerebral vasoconstriction is mediated by sympathetic fibers arising in the stellate ganglion and passing up along the internal carotid vessels, there has been a limited interest in treating new and even old cerebrovascular accidents by stellate ganglion block, with some favorable reports.|| In direct bilateral determinations of cerebral blood flow and oxygen utilization, however, Scheinberg [531] could demonstrate no significant difference in the values for the two sides either before or after a unilateral stellate block in normal young persons, persons with hypertensive vascular disease, and persons with acute cerebral thrombosis. Clinically most authorities appear to hold that the improvement sometimes noted following stellate ganglion block in cases of cerebrovascular accident more likely is simply a reflection of the wide range of spontaneous improvement possible in the natural history of such lesions. Wilson and his group [526] make the interesting suggestion that possibly any improvement following stellate ganglion block may result not from release of cerebral vasoconstriction, as to which doubt exists in many quarters, but rather from consequent improvement in the function of the heart and systemic circulation. It may be mentioned incidentally here that Hall,[532] in a study of psychosis due to cerebral arteriosclerosis in a series of 30 female patients using the sympatholytic drug benzazoline (Priscoline) in the hopes of relieving cerebrovascular spasm mediated through the stellate ganglion, failed to demonstrate any improvement in the cerebral function in any of the patients in the course of two months of observation. An unexpected finding was the beneficial effect of benzazoline in reducing the moderately elevated NPN values in these patients.

In the management of infraclinoid saccular aneurysms of the Circle of Willis and carotid-cavernous sinus aneurysms, Bassett and Gass [533] found that ligation of the internal carotid artery in the neck gave symptomatic improvement in the majority of 17 patients in whom the procedure was undertaken. Using carotid arteriography for diagnosis and then to follow the results of therapy, Ecker and Riemenschneider [534] demonstrated that no thrombosis occurred in an aneurysm of the internal carotid artery near its bifurcation after one hour of digital carotid

|| References 529 and 530.

compression. When a clip was placed on the common carotid artery so as to occlude the artery partially and reduce the mean carotid artery pressure by 50%, arteriography a week later showed 80% of the aneurysm obliterated. One month later a carotid arteriogram showed excellent filling of the internal carotid artery and its branches, with no definite evidence of residual aneurysm. A word of caution is injected by Shenkin and his group,[535] who found an average increase of cerebrovascular resistance of 47% in four cases after carotid ligation. There was a parallel mean systemic arterial blood pressure increase averaging 20%. No significant changes in cerebral blood flow and cerebral oxygen consumption were noted in three of the patients, but in the fourth these factors fell to very low levels and the patient became comatose and hemiplegic in eight minutes. The conclusion was reached that the desired reduction of the vascular pressure head in treating intracranial aneurysms by ligation may give rise to neurologic sequelae if cerebral blood flow is reduced proportionately. As a possible prophylactic against this hazard, Flothow [536] recommends prophylactic sympathectomy before ligation of any vessel; in the case of the internal carotid artery removing the inferior cervical and first and second thoracic ganglia and the trunk on the affected side.

There is increasing recognition of the part that duration and inadequate treatment of diabetes play in the onset of premature vascular disease, nephritis, retinitis, and coronary sclerosis in young diabetics. In a group of 282 patients whose diabetes began between the ages of 15 and 30 years Root and his associates,[537] in follow-up studies, have observed an incidence of some form of vascular disease in 71%. In those having the disease for less than 10 years, 21% showed calcification of arteries by x-ray, but in the group with duration of more than 20 years 88% showed calcified arteries in the legs or pelvis or occasionally the aorta. In persons in whom diabetes had been present for less than 10 years, nephritis appeared in 6%. After 10 years the incidence rose to from 20 to 25%. In the group of patients with duration of 10 to 19 years in whom control of diabetes had been poor retinitis was found in 65%, calcification in 78%, and nephritis in 40%. In the group with 20 to 29 years' duration the incidence of retinitis and calcification had risen to 90 and 96%, respectively, and nephritis occurred in 26%. In patients with diabetes of equal duration in whom control had been fair, strikingly lower incidences of complications were observed. In 34% of those whose diabetes had been present from 10 to 29 years blood pressure exceeding 150 mm. Hg developed, an impressive finding in view of the fact that these were relatively young patients.

In the treatment of arteriosclerosis of the lower extremities, Edwards and Crane [538] are of the opinion that lumbar sympathectomy offers far greater likelihood of improvement in the majority of cases than any other single method of treatment. Obviously not all patients may be expected to do equally well, but necrosis down to bone proximal to the toes is the only definite contraindication. The presence of diabetes, and to a certain extent of other visceral disease, including extreme hypertension or the previous loss of the other limb, renders a case less favorable but does not contraindicate sympathectomy. Age, sex, blood pressure levels between the extremes of high and low, level of occlusion of the major arteries, or degree of calcification of the arteries by x-ray give no information as to the ultimate results of the surgery. A good temperature response to a paravertebral or spinal anesthesia predicts a good result from operation, but failure to respond to

the test bears little or no relation to the final outcome. The careful observations of Pearl and Rosenman [539] are in general agreement, and LeFevre [540] finds sympathectomy valuable when conservative measures fail to prevent progression of the disease. Endarteriectomy for the treatment of chronic endarteritis obliterans uncontrolled by medical measures has aroused considerable interest. Reboul and Laubry [541] report on 93 endarteriectomies and state that complete relief was obtained in about half the cases. There were no signs to indicate that removal of the various layers of the vessel weakened the walls to a dangerous degree provided that the external elastic limiting layer was in a healthy condition. Nuñez and his co-workers [542] have also reported favorably on this technique. An ingenious method for regional heparinization after thromboendarteriectomy is described by Freeman and Gilfillan,[543] who insert a segment of polyethylene tubing into the proximal artery above the operative site. Postoperatively a continuous intra-arterial injection of heparin solution is passed under pressure through this tubing. Circulation was satisfactorily restored in six cases in which this method was used, and there were no hemorrhagic complications. One surgical procedure, however, which has been shown definitely to be of no value is end-to-end femoral arteriovenous anastomosis. Through extensive experimental studies in dogs, Palmer and Welch [544] have demonstrated that the end result of this maneuver differs little from the ordinary arteriovenous fistula. The increased pressure transmitted into veins and capillaries is definitely damaging to these vessels, without increasing blood flow to the tissues, since the shunted blood is quickly carried back toward the heart through collateral veins close to the site of anastomosis rather than flowing distally against the greater resistance offered by the capillaries.

In view of the time-honored and widespread use of the Buerger exercises in the conservative management of occlusive arterial disease of the lower extremities, the observations of Wilkins, Halperin, and Litter [545] are of importance. These authors demonstrated an increase in blood flow when the lower limb was in a dependent position by about 15% over the blood flow when the limb was in a horizontal position. They further noted a marked increase in the arteriovenous oxygen difference in the presence of even slight muscular activity. In view of these findings, the active muscular work of Buerger exercises may even be detrimental, by increasing oxygen demand in ischemic limbs. LeFevre [540] recommends elevation of the head of the bed by 6 in. (15 cm.), thus placing the lower extremities in moderate dependency and often relieving painful limbs. The oscillating bed, which administers so-to-speak passive Buerger's exercises, is effective when available.

Certain pharmacologic agents with vasodilating or sympatholytic properties, of which benzazoline and hexamethonium are the best known examples, have received clinical trial in various forms of peripheral vascular disease with some beneficial effect. Finnerty and Freis [546] consider hexamethonium to be approximately as effective as paravertebral sympathetic block, with advantages of easy administration and great potency. As DeBakey and his associates [547] point out, however, what is desired is vasodilatation of the affected extremity rather than vasodilation of the entire vascular tree, as occurs with these pharmacologic agents. Indeed, it is possible that generalized vasodilatation by reducing blood pressure may actually lead to a reduction to the flow of blood through an already ischemic extremity. In this connection, radioactive sodium studies measuring calf muscle

circulation have led Reese and others [548] to conclude that administration of benzazoline causes local shifting of blood in the lower extremities, with increased cutaneous flow and decreased muscular circulation. The authors conclude that this drug has no physiologic basis for use in intermittent claudication and peripheral skeletal muscle disorders. For persons in whom intermittent claudication is limiting but not crippling, Naide [549] emphasizes that simple reduction of the rate of walking from 110 to 120 steps per minute down to 90 to 105 steps per minute may permit very satisfactory extension of the patient's range before pain is experienced.

The use of anticoagulants in acute frostbite seems well established. According to Theis and his collaborators,[550] the early use of intravenous heparin interferes with the adhesiveness of agglutinating thrombi and thus may prevent thrombosis and gangrene in the early stages of recovery from acute frostbite. Anticoagulants also preserve the resorbability of the interstitial fluid forming in blisters and thereby prevent secondary fibrous tissue formation during healing. Anticoagulant treatment of frostbite to be effective must be both early and resolute. In any peripheral vascular condition in which both anticoagulant therapy and paravertebral sympathetic block might both play a useful role it is well to remember the potential hazard of hemorrhage when these two forms of therapy are combined. Cole and Kleitsch [551] describe a case of retroperitoneal hemorrhage following lumbar block in a patient with prothrombin time approximately double that of the control, presumably resulting from unavoidable perforation of a lumbar vein during paravertebral injections. Admitting that awkward choices may be posed to the clinician, the authors feel that in frostbite it is probably wiser to use one or the other form of treatment and not to combine the two. For arteriosclerosis with impending gangrene the wisest course is to perform lumbar sympathectomy and follow with anticoagulant therapy in the postoperative period.

The beneficial effect of complete abstinence from tobacco in thromboangiitis obliterans is demonstrated by the case of Gifford and Hines,[552] in which a 12-year "clinical cure" was observed following complete omission of tobacco. It has not been possible to determine whether improvement accompanying abstention from tobacco derives primarily from arresting the disease process in the arteries and veins or whether circulation is bettered merely by relaxation of unaffected arteries.

Of great interest in connection with the problem of thrombophlebitis is the description by D'Alessandro [553] of a new clinical sign for the early detection of venous thrombosis of the lower extremity. The phenomenon, said to be invariably present even in the absence of other appreciable signs or symptoms of thrombosis, is that of marked diminution or even absence of the femoral pulse in the affected extremity. The physiologic mechanism underlying this sign is the marked and early angiospasm that attends all vascular accidents to any extremity, regardless of the location of the thrombus. The change in the femoral pulse occurs early in both thrombophlebitis and phlebothrombosis, long before there is any demonstrable edema or swelling, and therefore affords a simple bedside test for early recognition of these serious complications. That spontaneous thrombophlebitis may occur in apparently healthy persons, without being preceded by trauma, infection, heart failure, cancer, operation, or other precipitating episodes, has become increasingly the subject for comment.¶ In such spontaneous cases there is a relatively high

¶ References 554, 555, and 556.

incidence of involvement of the right lower extremity, of superficial phlebitis, and of recurrence. According to Crane,[555] the chief causative factor in the appearance of venous thrombosis in the lower extremity occurring in active healthy persons is some antecedent effort or strain which results in injury to the wall of a main venous trunk with thrombus formation at the site of the injury. Having observed the phenomenon of spontaneous venous thrombosis only in persons of over 6 ft. (1.8 meters) in height, Naide[556] suggests that the greater vein length in tall persons may increase the difficulty of venous return to the vena cava, thus predisposing to stasis. In addition, the cramped positions that tall persons are frequently forced to assume for considerable periods of time, especially when sitting, may be a contributing factor. The association of superficial thrombophlebitis, characterized by thrombosis of a vein with little evidence of inflammatory reaction and subsidence within a few days, with carcinoma of the lung has been stressed by Fisher and others.[557] Occurring principally in males, recurrent thrombophlebitis should be considered as a warning sign of hidden carcinoma, regardless of the location, mildness of intensity, or shortness of duration of the second attack of phlebitis. It has been further observed that in such cases adequate anticoagulant therapy may not suffice to prevent further thrombotic phenomena, a finding which again should suggest the presence of carcinoma and which further indicates that the phenomenon of thrombophlebitis is possibly related to some change in the coagulability of the blood which must occur in such instances of carcinoma.

In the prevention of embolic complications from venous thrombosis after surgery, Leithauser and his associates[558] emphasize that there is no substitute for early ambulation and frequent leg exercises. Outlining what by ordinary standards is a most rigorous and standardized regimen embodying these principles, the authors state that in a series of 3,371 surgical cases, 90% of which were abdominal operations and at least 1,631 represented so-called major surgery entailing greater hazard of embolic complication, there was no instance of pulmonary embolization, either fatal or nonfatal. It is the authors' contention that observers who profess to adhere to a program of early ambulation but continue to experience instances of thromboembolic complications have simply failed to apply the several techniques involved with sufficient vigor and persistence. As a less demanding approach to the problem of prophylaxis of thromboembolic disease in hospital patients, Wilkins and his group[559] have shown that the wearing of elastic stockings is practical as a routine procedure and does no harm if care is taken to apply the stockings loosely (at 10 to 15 mm. Hg pressure) and to omit them altogether in cases with ischemic vascular disease in the legs. Significant reduction in the incidence of fatal and nonfatal pulmonary embolism was demonstrated following the use of such stockings. In another although somewhat less practical study Tichy and Zankel[560] observed only one instance of venous thrombosis after operation in a group of 639 patients in whom rhythmic contractions of the calf muscles were induced by means of electrodes placed around the legs.

The use of vein ligation as a prophylaxis for pulmonary embolism has distinctly decreased in favor during the last few years. In an intensive study of a five-year large-scale program Roe and Goldthwait[561] concluded that femoral vein interruption failed to alter the mortality figures for pulmonary embolism as compared to earlier similar periods during which this procedure was not performed. On the

basis of postmortem studies Moran [562] states that the high incidence of pulmonary embolism due to prostatic vein thromboses suggests that anticoagulant therapy should be more effective than venous ligation in the prevention of pulmonary emboli, at least among nonsurgical patients in the older age group and particularly those suffering with cardiovascular disease of other types. The use of the anticoagulant sodium polyanhydromannuronic acid sulfate (Paritol C), a synthetic heparinoid, in surgical cases has been described by Martin and Boles.[563] This agent effectively raises the clotting-time levels for 8 to 16 hours and may prove to have a distinct place in the prophylaxis of postoperative venous thrombosis. The inadequacy of superficial vein ligation and at times even of anticoagulant therapy is illustrated by the patient of Pratt [564] in whom the control of multiple pulmonary emboli was obtained only by inferior vena cava ligation. That vena cava ligation is a last resort, however, is underlined by the study of Shea and Robertson,[565] who showed that of a group of 25 patients undergoing caval ligation only one was entirely free from adverse results and that the capacity for carrying out either previous or adequate means of livelihood was interfered with in 9 patients. None of the patients experienced subsequent pulmonary infarction, but a small group showed primarily arteriospastic phenomena leading eventually even to reflex dystrophies, while in the majority edema was the outstanding sequel, either transient or persistent, in the latter case starting the sequence of increased interstitial tissue protein, fibrosis, dermatophytosis, and eventual ulceration. The authors assert that caval ligation should not be used for the prophylaxis of thromboembolism but should be reserved specifically for the patient who has experienced multiple infarctions, is dangerously ill, and in whom other measures for the treatment of thromboembolism have failed. For the patient in whom massive pulmonary embolism and its consequences are the presenting problem, Faxon, Flynn, and Anderson [566] advocate stellate ganglion block. When done within a few hours of the acute episode this maneuver promptly relieves symptoms, presumably owing to the abolition of reflex spasms secondary to pulmonary embolization. It is further possible that the relief of spasms may diminish the area of lung which subsequently becomes infarcted. If stellate block is delayed 12 hours or longer after embolism, however, little or no improvement may be expected, either because the spasm has subsided already or because the effects of the occlusion has become too firmly established.

In cases of severe postphlebitic lymphedema in which it can be assumed that the perforator veins are grossly incompetent and that the orthostatic venous hypertension cannot be overcome by the pumping action of muscular contraction in the lower part of the leg, Scott [567] reports excellent clinical results from use of a technique involving pulsatile air pressure. A legging of inelastic material containing an inflatable rubber bladder is applied to the affected leg and the bladder then pumped up, applying a controlled and uniform pressure throughout the area covered by the bladder. When the patient walks there is a rhythmical rise in the pressure with each contraction of the muscles. In essence a substitute for the deep fascia has been placed outside the skin and subcutaneous tissues, and the powerful pumping action of muscular contractions compressing the veins and pushing the blood upwards against gravity is applied by this means to the superficial veins throughout the lower part of the leg. The swelling and induration secondary to postphlebitic or varicose stasis in the lower leg can be controlled, and most instances of postphlebitic

and varicose ulcers are regularly healed while the patient is ambulatory. An occasional deep ulcer may require split thickness skin grafting, and virulent surface infection when present must be repressed before the pulsatile air pressure technique can be successfully applied. It must be emphasized that this legging is a mechanical appliance, which overcomes venous stasis only while it is in use. The damage to valves in varicose veins or in the postphlebitic state is usually a permanent one, and as a result use of the legging must similarly be on a permanent basis in most cases, although a patient with the usual good result may be allowed to go without the legging up to 25% of the time he is up and about on his feet, or at any time that he is willing to keep his foot elevated to body level.

Since its introduction several years ago the artificial kidney has been shown to have a number of therapeutic applications to certain clinical syndromes in addition to its obvious usefulness as a research instrument.[568] It is of great value in acute complications of acute anuria such as potassium intoxication and pulmonary edema and of some value as an adjunct to conservative therapy in prolonged uncomplicated anuria. In properly selected cases it may help in the preparation of the chronic uremic patient for surgery and the rehabilitation of the chronic nephritic patient; in rarer instances of renal insufficiency, particularly the hepatorenal syndrome, with hyperpyrexia and hypotension refractory to replacement therapy, hemodialysis may be effective. As Snapper and Schaefer[569] point out, however, nondialyzable toxic substances may also play a role in the etiology of uremia. These workers report two patients suffering from an hepatorenal syndrome, with extreme oliguria and severe uremia following hepatitis, in whom exsanguinotransfusion was followed in each instance by diuresis and the ultimate recovery of the patient. In these cases 7 to 8 liters of citrated blood were administered to the patients, with subsequent withdrawal of an equal volume of blood. The amounts of alkali which the citrated transfusion blood contains also may be an additional favorable measure in view of the acidosis which is to be expected in such cases.

Most recently cross transfusion has been introduced by Salisbury and others # for the treatment of acute nontransmissible diseases of internal organs wherein temporary improvement may provide a better chance for spontaneous recovery to occur. In dog experiments cross transfusions begun within 90 minutes after the intravenous administration of mercuric chloride to one animal were successful in keeping the potentially poisoned animal clinically well, with normal or nearly normal levels of creatinine. In a few human cases, exchanges of volumes of blood up to 25 to 52 liters are reported. In one patient with the nephrotic syndrome, a single cross transfusion produced a remission still maintained at the time of reporting. Distinct symptomatic improvement, accompanied by a significant reduction of blood pressure, occurred in a case of uremia due to malignant hypertension and in two cases of chronic glomerulonephritis, although in all cases the patients eventually died. The full potentialities and hazards of this technique remain to be evaluated.

SUMMARY

In summary, brief emphasis may be laid on the major trends and progress of the period of this review. The surgery of congenital cardiovascular defects and of rheumatic valvular deformity has demonstrated that an increasing variety of lesions

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can be safely palliated or corrected; the advent of mechanical heart substitutes and hypothermic techniques suggests that an even more striking series of advances in the surgical field is at hand. The several hormonal agents active in the rheumatic state have therapeutic limitations but as research tools are highly useful. Detailed anthropological and biochemical observations offer promise in defining more clearly the processes of atherosclerosis and arteriosclerosis, and some hope is justifiable that increasingly effective therapeutic measures, particularly hormonal, are forthcoming. Vectorcardiography and ballistocardiography are receiving widespread attention and promise detailed aid in the evaluation of the cardiac patient. In the field of hypertension the concepts of a changing vascular reactivity and of deficiency of depressor agents rather than surfeit of vasoconstrictor substances point to new areas of potentially productive research. The National Heart Institute, created in 1948, has continued to provide a vital impetus to the advancement of cardiovascular research and its clinical application.

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Case Reports

ACUTE BLASTOMYCOTIC PNEUMONIA

Report of a Fatal Case of Short Duration Diagnosed by Needle Biopsy of Lung

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MANY CASES of blastomycosis of short duration have been recorded in which pulmonary involvement and distant hematogenous spread to the brain, bones, and skin were demonstrable.* Few cases with disease limited to the lung have been reported. The following case of pulmonary blastomycosis is unusual because of its rapid fulminating course with limitation to the lung proper and because of the failure of usual laboratory techniques to establish a diagnosis. Clinicians who saw the patient during his hospitalization were about equally divided into those who thought that the widespread pulmonary disease represented a rampant neoplastic process and others who believed that the condition was infectious. Only after a needle biopsy of the lung did the true etiology become apparent.

REPORT OF A CASE

A 36-year-old Negro male foundry worker entered the Veterans Administration Hospital, Hines, Ill., on Feb. 13, 1953, with complaints of chills, fever, cough, and weakness. Two months before admission, he had the "flu." Following this he felt ill, was disinclined to activity, had intermittent chills and fever, and developed dyspnea. He was seen by his local physician, who gave him penicillin injections three times weekly for one month. The fever persisted, and the patient developed a cough, with expectoration of copious quantities of grayish-yellow sputum which was occasionally blood-streaked. He estimated the sputum to be in excess of one cupful (0.24 liter) per day. He began to lose weight; it dropped from 205 to 175 lb. (92.2 to 78.7 kg.) in two months. After one month of penicillin therapy the chills and fever had abated but the productive cough and dyspnea persisted. The patient was advised to have a chest roentgenogram, following which he was told that he had pneumonia, whereupon he reported to this institution.

Past history revealed that the patient had always been a foundry worker with extensive exposure to silica dust. A detailed accounting of his various occupations and materials used did not reveal any known exposure to beryllium. There was no history of any cutaneous lesion. In 1946 the patient was hospitalized, in Pennsylvania, with symptoms of cough and hemoptysis for a period of two months, and hospital records indicate that he was treated for left lower lobe pneumonia and acute fibrinous pleurisy. An extensive work-up at that time revealed no evidence of tuberculosis; on discharge from the hospital the patient's chest film showed no abnormalities. During military service he was stationed in Kentucky, Arizona, and Arkansas, and while overseas he worked as a gasoline truck driver in Germany, France and England. His mother died following "surgery for a tumor," and his father died of unknown cause. There was no known hereditary or familial disease.

From the Veterans Administration Hospital (Medical Service).

* References 1 and 2.

Physical examination at the time of admission revealed a muscular 36-year-old Negro man who was acutely ill and markedly dyspneic at rest. The temperature was 101.8 F., pulse rate 116, and respiratory rate 28. He showed evidence of recent weight loss and was perspiring profusely. Examination of the eyes, ears, nose, throat, head, and neck showed no abnormalities except for pallor of the mucous membranes and conjunctivae. The only palpable lymphadenopathy was in the right axilla, where two small rubbery freely movable nodes were felt. The thorax was symmetrical, with considerable inspiratory lag on the left side. The chest was flat to percussion over the left side posteriorly and laterally, with normal resonance on the right. Breath sounds were absent in the posterior portion of the left chest, with tubular breath sounds just above this area. Bronchovesicular breath sounds were heard in the apical portion of the left chest and over the entire right chest. A few scattered moist rales were heard in the lower

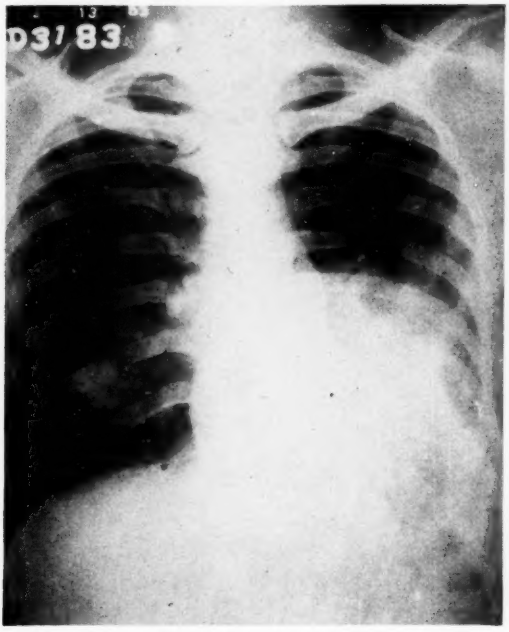

Fig. 1.—Acute Blastomycotic pneumonia (on admission).

portion of the right lung and in the middle portion of the left lung field posteriorly. Diminished tactile fremitus was noted in the lower posterior chest bilaterally. Examination of the cardiovascular system was negative except for tachycardia. The blood pressure was 110/65 in the left arm. The remainder of the physical examination showed no abnormalities.

Laboratory Examination.—On admission the erythrocytes numbered 2,500,000 per cubic millimeter and the white blood cells numbered 30,000 per cubic millimeter with 81% neutrophiles, 16% lymphocytes, 2% monocytes, and 1% eosinophiles. The hemoglobin was less than 7.5 gm. per 100 cc. Repeated blood cell counts did not show any appreciable change from these values. The urine on admission had a specific gravity of 1.020 and contained a faint trace of albumin, no sugar, and several red and white blood cells per high-power field. Subsequently the urine had a specific gravity of 1.012 and contained a trace of albumin, no sugar, 40 white blood cells and 5 red blood cells per high-power field. Determinations for Bence-Jones protein were negative, as were urinary assays for prolan A. The erythrocyte sedimentation rate (Cutler) was 32 mm. in an hour. The bisulfite and CO_2 tests for erythrocyte sickling were negative. Repeated smears and cultures of sputa, gastric washings, and tracheobronchial secretions obtained at

bronchoscopy were negative for acid-fast bacilli, yeasts, and fungi. Cell blocks of material obtained at bronchoscopy were examined microscopically and were found to contain no tumor cells. Sputum cultures for predominating organisms grew alpha hemolytic streptococci and Neisseria catarrhalis. The nonprotein nitrogen was 24.7 mg. and the blood urea nitrogen was 10.8 mg. per 100 cc. The total protein was 5.6 gm., with albumin 2.9 gm. and globulin 2.7 gm. per 100 cc. The fasting blood sugar was 86 mg. per 100 cc. The electrophoretic pattern (Tiselius) of the serum proteins was normal. The alkaline phosphatase was 4.8 units (Bodansky), and the acid phosphatase was 0.4 units. Blood cultures, including several special cultures for Brucella, were negative. The heterophile antibody test was negative, as were agglutinations for typhoid O and H, paratyphoid A and B, Proteus OX-19, Brucella, and cold agglutinins. The urinary 17-ketosteroid excretion for 24 hours was 7.32 mg.

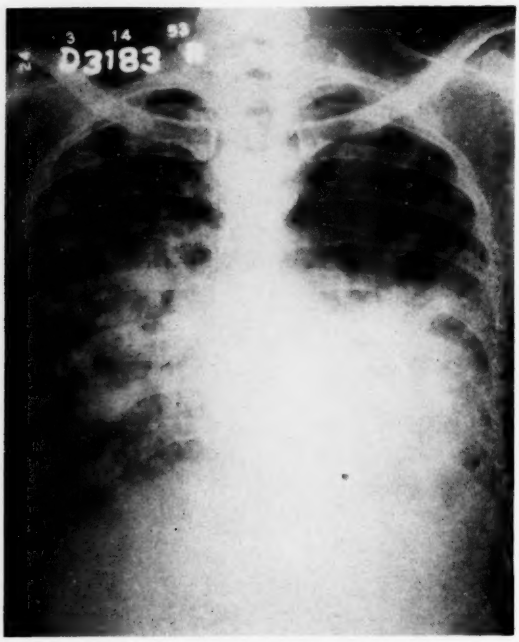

Fig. 2.—Acute Blastomycotic Pneumonia.

The first thoracic roentgenogram, performed on the day of admission (Fig. 1), revealed a patchy infiltration of the right lung with suggestive nodular densities. There was an homogeneous infiltration obscuring the lower half of the left lung. Repeat posteroanterior and left lateral Bucky views revealed consolidation of the lower lobe of the left lung. Repeated examinations showed rapid progression of the lesions. A film (Fig. 2) taken 29 days after the previously described film revealed an extensive nodular infiltration and marked progression of the patchy infiltration of the right lung. An intravenous pyelogram revealed normal kidneys, ureters, and urinary bladder. An upper gastrointestinal series, barium enema, and skeletal survey showed no abnormalities. Sternal marrow examination was interpreted as consistent with a leukemoid reaction.

Hospital Course.—On admission the patient was placed on bed rest and therapy was started with intramuscular procaine penicillin 600,000 units twice daily. After seven days the patient showed no signs of improvement, whereupon therapy with chlortetracycline (Aureomycin) 500 mg. every six hours was instituted, without avail. Skin tests with PPD, coccidioidin, histoplasmin, and blastomycin were negative. On the fourth hospital day thoracentesis of the

left pleural cavity was attempted, but no fluid could be withdrawn from any of several sites. On the 12th hospital day, bronchoscopy was performed and thick mucoid secretions were encountered from both major bronchi, but in greater quantity from the right. The bronchial mucosa was markedly reddened in some areas. No tumor was seen, but the carina seemed slightly blunted on this examination. Fluoroscopy showed immobility of the left diaphragm, and the diagnosis of bronchogenic carcinoma or metastatic malignant tumor was considered more seriously. Repeat bronchoscopy was performed on the 21st hospital day, and the findings were unchanged from the examination approximately two weeks earlier.

During the entire hospital course the patient continued febrile, the temperature spiking daily to 101 to 103 F. His condition became more critical, and after the second bronchoscopy he required oxygen for severe dyspnea. At this time it was impossible to be sure whether the

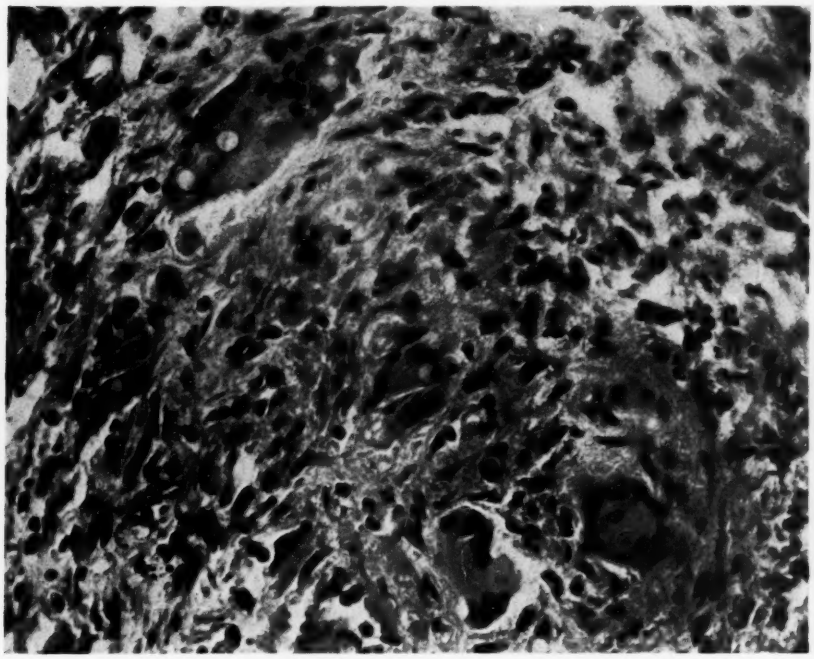

Fig. 3.—Blastomycosis of lungs (aspiration biopsy specimen).

patient's downhill course was due to secondarily infected malignant tissue or to a primary bacterial or fungus infection which might be amenable to therapy. Earlier in the patient's course a wedge biopsy of the lung was contemplated, but the thoracic surgery service believed that the patient was too ill for the procedure. Therefore, on the 23rd hospital day, an aspiration biopsy of the lower lobe of the left lung was performed. On microsection, lung tissue with doubly refractile organisms could be seen (Fig. 3). The diagnosis of blastomycosis was established, and therapy with intravenous 2-hydroxystilbamidine was instituted. In spite of oxygen and supportive therapy, the relentless dyspnea persisted, the nail beds became deeply cyanosed, and the patient died on the 29th hospital day.

Autopsy Observations.—At autopsy a well-developed Negro man 185 cm. in length was observed. Body weight was 170 lb. (76.5 kg.), with evidence of considerable weight loss.. The initial incision revealed very sparse subcutaneous fat. There were no pleural adhesions except over the left diaphragm, where the visceral pleura was firmly adherent. Each pleural cavity contained approximately 600 cc. of straw-colored fluid, which was negative for yeast, fungi, and

bacteria on culture. The left lung weighed 2,000 gm. and the right, 1,300. Both lungs were of firm consistency, with little crepitation. The surfaces were studded with subpleural nodular densities of varying size. On cut section the entire exposed surface was studded with yellowish-white nodules varying from 3 to 6 mm. in diameter. Some sanguinous and sanguinopurulent exudation appeared on the cut surface. Subsequent culture of this exudate grew Blastomyces dermatitidis. The mediastinal lymph nodes were not enlarged, but the peribronchial and peritracheal nodes were minimally enlarged.

There was no hepatic, osseous, or cutaneous involvement, and the remainder of the autopsy showed no abnormalities. Microscopic examination of tissues and organs removed revealed that the organic involvement in this patient was limited to the lungs. The histologic diagnosis was "pulmonary blastomycosis, bilateral, fulminating."

COMMENT

A thorough search through this patient's past and occupational history gives no clue as to the source of infection. In the absence of bone and skin lesions it is reasonable to assume that the infection was primary in the lungs and did not result from metastatic spread. The usual source of infection is by contact with B. dermatitidis as it occurs in nature, and little is known about its habitat and actual spread.[3] It is well known that occasional cases of blastomycosis have occurred in laboratory workers and in pathologists who have performed autopsies on patients with the disease, but there is little evidence to support the thesis that it is often acquired by contact with either sputum or skin lesions in patients suffering from the disease.

Our patient's disease progressed rapidly to a fatal termination, and because of the rather long prodromal period it is impossible to estimate its duration exactly. Our detailed knowledge extends only over the 29-day period of his hospitalization. Baker and co-workers report a case of 20 days' duration, in a white woman, and mention another case, in a Negro woman, of three and one-half months' duration.[4] Bonoff reported 23 cases of acute pulmonary blastomycosis occurring in Army personnel on Okinawa. Six of the cases reported had positive roentgenographic findings, and in one fatal case autopsy was done, showing characteristic features of blastomycosis.[5] In a review of the literature, Martin and Smith observed that the average duration of the disease in fatal cases was less than six months in 20 of 91 cases; however, no statement was made regarding the case of shortest duration. The remaining 71 patients lived varying periods of time, from six months to more than three years.[1]

Patients with fulminating blastomycosis present a problem in differential diagnosis. In the above-reported case the initial working diagnosis was pneumonia, but only the normal respiratory flora could be cultured from both sputa and tracheobronchial secretions obtained at bronchoscopy. Biopsy of the mucous membrane of the respiratory tree was of no value nor were cultures obtained from gastric washings. The diagnosis was established only after microsections of material obtained by aspiration biopsy of the lung were examined, in which the characteristic doubly-refractile organisms of B. dermatitidis were seen. The diagnosis was subsequently further substantiated by culture of the organism from exudate obtained from the cut surface of the lung at autopsy.

We wish to emphasize the value of aspiration biopsy in this case and its possible application in other cases of pulmonary disease of undetermined etiology. The value of liver biopsy with the Vim-Silverman needle is unquestioned; it has also been useful in biopsy of the thyroid, pancreas, kidney, and other organs.[6] The procedure

for aspiration biopsy is equally simple and can be performed, as in this case, with an ordinary 6 in. (15 cm.) 18-gauge needle with stilet (a 15- or 16-gauge needle may be used). After preparation of the skin, the determined interspace is anesthetized with procaine hydrochloride and the needle is introduced into the pleural space. If it has been previously determined fluoroscopically that the diaphragm is immobile, the stilet is removed and the needle may be introduced into the lung and suction applied with a 20 cc. syringe. If, however, the diaphragm is mobile, it is wise to have the patient inhibit respiration before and during introduction of the needle into the lung. Biopsy specimens from lesions in the periphery of the lung

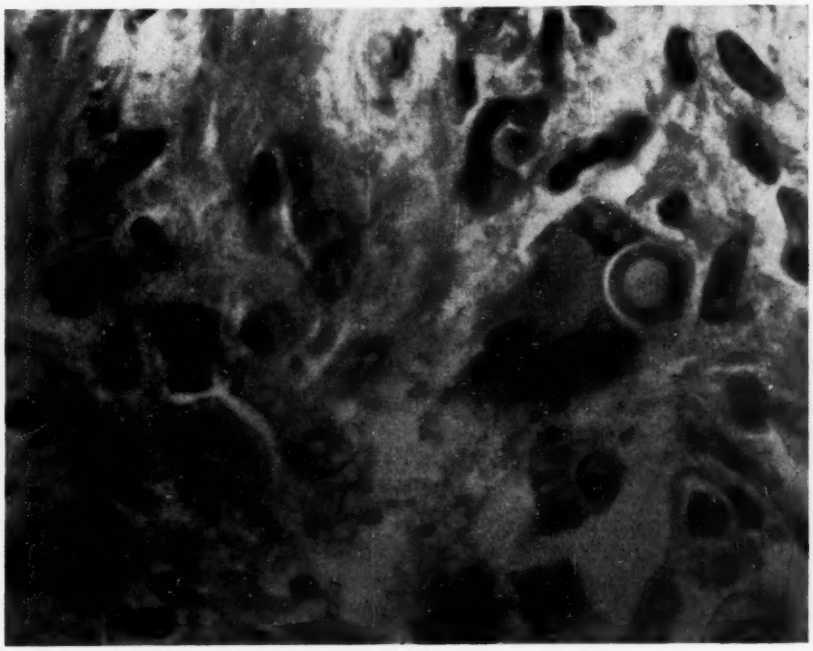

Fig. 4.—Blastomyces dermatitides (note doubly refractile sphere).

can easily be acquired by this technique, and some have utilized the procedure for lesions at or near the hilum, but this is deemed hazardous.

This patient received antibiotic therapy before admission to the hospital and subsequently received large doses of both penicillin and chlortetracycline. The question of the role of antibiotics in the production of overgrowth of fungi in the oral cavity and lungs has been raised.[7] It is possible that these drugs permitted the rapid overgrowth of fungi in this case which accounted for its fulminant fatal course. These same drugs were also used in the rapidly fatal case reported by Baker and co-workers.

The mortality from systemic blastomycosis is high. From what few data are available, other similar cases of blastomycosis limited to the lungs progressed rapidly to fatality and, of those few reported, the mortality was 100%. Probably no true

estimate of the number of fatal acute cases can be made, since many undoubtedly terminate without recognition of the etiology. No definite over-all mortality figures can be found for the systemic chronic form of the disease. The disease seems to be more common in the Negro and is definitely more common in males.

The pathologic picture in the lung varies with the stage of the disease. In acute cases the lung is consolidated and purulent exudate abounds; the chronic form tends to abscess formation. The pleura is invariably thickened and is frequently involved in the inflammatory process. The consolidated areas assume a nodular appearance, with either large nodules or small ones resembling those of miliary tuberculosis. The characteristic morphology of the organism is easily recognized histologically (Fig. 4). In our patient both the needle biopsy and autopsy sections showed innumerable free and engulfed forms (some giant cells contained more than 20 organisms). Careful search did not disclose the presence of the small forms of Blastomyces reported by Tompkins and Schleifstein [8] and others. Cultures can be grow on either Saboraud's agar or, preferably, Littman's ox-gall agar at room temperature or on blood agar at incubator temperature.[9]

THERAPY

Cure of patients with blastomycosis depends upon the extent and duration of the disease and upon the immunologic response of the patient. Reports of cures are appearing with increasing frequency in the literature. The etiologic agent is the same in both the systemic and cutaneous forms of the disease, but the systemic form carries a higher mortality. The patient with the positive skin reaction to Blastomyces extract and negative complement-fixation tests has the worst prognosis. All patients should be skin tested, both as a diagnostic and as a prognostic aid. The technique is the same as for the intradermal skin test for tuberculosis, and occasionally, as in our case, negative results are obtained in patients with the disease, but false-positive reactions are unreported.

Probably the oldest form of therapy is with iodides. Iodide therapy should not be undertaken until the patient's sensitivity has been determined. This is a reason additional to those mentioned above for performing the intracutaneous skin test in suspected cases. If the patient reacts violently to the intracutaneous injection of standardized heat-killed vaccine of B. dermatitidis, therapy with iodides should not be started until the patient has been hyposensitized. This can usually be accomplished with either an autogenous vaccine or with a vaccine made from any other strain. Usually a 1 : 1,000 suspension in isotonic sodium chloride solution is injected, starting with a 0.1 cc. dose. Every other day the vaccine is injected, in increasing amounts, until 1.0 cc. is reached. The dosage is then either maintained at 1.0 cc. subcutaneously every other week or decreased to 0.5 cc. given at the same time interval. After several weeks, therapy can be started with saturated solution of potassium iodide given in 3 drop (0.19 ml.) doses three times daily and gradually increased 1 drop (0.06 ml.) at a time to tolerance.

X-ray therapy has been recommended for the skin lesions either separately or in conjunction with local excision, and x-ray therapy with surgical drainage has been used for bone lesions.

Penicillin has been reported as beneficial in the treatment of blastomycosis, as have all the other currently used antibiotics. The general consensus of opinion is

that these drugs are of no benefit and may possibly be deleterious. Benedek, however, reports a cure with 9,000,000 units of penicillin in an extensive progressive case of blastomycosis of three years' duration.[10]

Corticotropin (ACTH) and cortisone have been unsuccessfully used in the treatment of blastomycosis. The results seem to be similar to results seen with these drugs in tuberculosis.

The drugs showing the greatest promise at this time are the diamidines: stilbamidine, 2-hydroxystilbamidine and 4-4 diamidinodiphenoxypropane (Propamidine). Colbert reported a case of cutaneous blastomycosis treated with Propamidine with satisfactory results.[11] Cummins, Bairstow, and Baker reported favorable response with stilbamidine in two cases at this institution.[12] Noojin recorded good response in one patient with cutaneous and two with systemic blastomycosis treated with stilbamidine. Fink and co-workers report successful treatment of one case of cutaneous blastomycosis with stilbamidine.[13] Schoenbach and co-workers reported a case of systemic blastomycosis treated with stilbamidine with favorable results.[14] Unfortunately, our patient's condition was preterminal before the diagnosis was established; however, one dose of 300 mg. of 2-hydroxystilbamidine was given intravenously before his death.

Noojin and Fink both report severe neuropathy of the fifth cranial nerve following the use of stilbamidine. This same phenomenon has been observed at this hospital in patients treated with stilbamidine for coccidioidomycosis and by Snapper and co-workers.[15]

Stilbamidine is injected intravenously in the form of stilbamidine di-isethionate, containing 54% stilbamidine. An average of 15 to 20 daily doses of 100 to 150 mg. are given. 2-Hydroxystilbamidine is equally efficacious but far less toxic. These drugs probably offer the greatest benefit to patients suffering from this disease, but they must be used in a greater number of cases before their definitive value in the treatment of blastomycosis can be assessed.

SUMMARY

A case of fulminating pulmonary blastomycosis without evidence of hematogenous spread is reported.

The value and technique of aspiration biopsy of the lung as a diagnostic aid is discussed.

In acute infectious diseases of the chest, acute blastomycosis must be considered in the differential diagnosis.

The therapy of blastomycosis is reviewed.

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News and Comment

ANNOUNCEMENTS

Problems of Gerontology.—A symposium on the Problems of Gerontology under the auspices of the Johns Hopkins University School of Hygiene and Public Health and The National Vitamin Foundation will be held at the Biltmore Hotel, Madison Avenue at 43rd St., New York, Tuesday, March 2, 1954.

The speakers for the morning session will be Dr. Nathan W. Shock, Dr. Albert I. Lansing, Dr. H. J. Deuel Jr., Dr. Charles S. Davidson, and Dr. Bacon F. Chow; the chairman will be Dr. Bacon F. Chow.

Speakers for the afternoon session will be Dr. John Esben Kirk, Dr. Frank H. Bethell, Dr. C. N. H. Long, Dr. Dwight J. Ingle, Dr. Henry A. Rafsky, and Dr. Nathan W. Shock, chairman.

Further information regarding the Symposium may be obtained from the National Vitamin Foundation, 15 E. 58th St., New York 22.

Establishment of Russell M. Wilder Fellowship.—The National Vitamin Foundation invites persons holding doctorate degrees in medicine or one of the biological sciences, who are interested in continuing their training in the science of nutrition, to become candidates for the newly established Russell M. Wilder Fellowship.

This doctorate fellowship was created by the Foundation to honor Dr. Russell M. Wilder, of the Emeritus Staff of the Mayo Clinic and former associate editor of the A. M. A. Archives of Internal Medicine, for his more than forty years of devoted service and significant contributions to medicine and public health and particularly for his leadership in advancing our knowledge of diseases of metabolism and nutrition.

In establishing the fellowship, the Foundation expresses its feeling of deep appreciation to Dr. Wilder for his pioneering work and provides, upon his retirement, an opportunity to a qualified young scientist to equip himself for a career inspired by Dr. Wilder's example. The fellowship is one more important step taken by the Foundation in its continually growing program, directed to the purpose that the health and welfare of mankind may be improved through better nutrition.

1. The Fellowship is for three years and pays the recipient $4,500 the first year, $5,000 the second year, and $5,500 the third year. It becomes effective Sept. 1, 1954.

2. Application forms can be obtained from the offices of The National Vitamin Foundation, 15 East 58th St., New York 22.

3. Candidates must mail their completed application forms to the Foundation on or before March 15, 1954.

4. Applications must be accompanied by a letter from the executive officer of the institution where the work is to be done and by a letter from the head of the department under which the candidate is to work, attesting to the fact that the candidate will be permitted and encouraged to carry on his work and studies in the institution and department indicated.

5. The candidate must outline a program of investigation, which must be approved by his preceptor.

6. The candidate must give reasonable assurance that he will complete his fellowship and continue to work in the field of nutrition following the period covered by the fellowship.

7. The successful candidate will be chosen by The National Vitamin Foundation's Scientific Advisory Committee. Applicants will be notified of action taken on or before July 1, 1954.

American College of Physicians.—The American College of Physicians will meet in Chicago April 5-9, 1954, with headquarters at the Conrad Hilton Hotel.

Program will consist of General Scientific Sessions, Symposia, Color Televised Clinics, Panel Discussions, and Clinical-Pathological Conferences. Speakers and participants will be carefully selected authorities in the several fields of internal medicine and allied specialties, including pediatrics, dermatology, and others.

Qualified physicians may attend this session as visitors if sponsored in advance by letter or in person by a member of the College; such physicians shall pay a registration fee. Bona fide hospital residents, regardless of their location in North America, may be admitted without fee upon presentation of proper credentials from their hospitals. Members of the Medical Corps of the Army, Navy, Public Health Service, Air Force, and Veterans Administration, either of the United States or of Canada, may also be admitted free upon presentation of proper credentials.

American Goiter Association Meeting.—The 1954 meeting of the American Goiter Association will be held at the Somerset Hotel, Boston, April 29-May 1, 1954. The program for the three-day meeting will consist of papers and discussions dealing with the physiology and diseases of the thyroid gland.

Fourth Congress of the Association of European and Mediterranean National Societies of Gastroenterology.—This meeting will be held in Paris June 27-July 2, 1954, under the chairmanship of Dr. R. A. Gutmann.

The subjects to be dealt with are portal hypertension and dumping syndrome.

Three sessions will be devoted to the reading of general reports and discussions of them.

Portal physiology
Exploration of pressures and rates of circulations in the portal vein
Portal radiology
Signs, diagnosis, and treatment of portal hypertension from extrahepatic block
Signs, diagnosis, and treatment of portal hypertension from intrahepatic block
Acute thromboses of trunk and branches of the portal vein
Circulatory modifications due to portal hypertension (excluding esophageal varices)
Physiopathology of portal shunts
Dumping syndrome: definition and clinical syndrome
Biologic syndrome of dumping syndrome
Etiological relation of surgery to dumping syndrome
Pathogenesis and treatment of dumping syndrome

A Congress of the Association of Physiopathological Studies of the Liver and Nutrition will immediately follow the Fourth Congress and will be held at Vichy under the chairmanship of Dr. R. A. Gutmann, July 2-5. The subject will be biliary dyskinesia.

Festivities at Vichy are to include tours of the historic monuments of the region, a gala theatrical representation, and dinner at small tables in the Grand Casino of Vichy.

The Wata Travel Agencies are in charge of all tourist organization of the Congress and can furnish all necessary information in all foreign countries.

Regional Meeting of the National Gastroenterological Association.—A regional meeting of the Central Region of the National Gastroenterological Association will be held in Milwaukee, Sunday, March 28, 1954. The scientific sessions will be held at the Hotel Schroeder, at 2:00 p. m., following the semiannual meeting of the Association's National Council.

The Central Region is comprised of the states of Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin.

Members of the medical profession are invited to attend. A copy of the program may be obtained by writing to Dr. Joseph Shaiken, 536 W. Wisconsin Ave., Milwaukee 3, or to the Secretary, National Gastroenterological Association, 33 W. 60th St., New York 23.

Books

Textbook of Pharmacology. By William T. Salter, M.D. Price, $15.00. Pp. 1,240, with 284 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1952.

Those familiar with the important original contributions of Dr. Salter to present knowledge of physiology and the action of drugs will be excited over this new textbook of pharmacology. It is in no sense a handbook for quick reference in busy office practice. On the other hand, it is a gold mine of important fundamental information for the student and thoughtful practitioner who wishes to know the reasons behind the therapeutic measures he is using. Physiologic mechanisms are dealt with in a painstaking but thoroughly understandable manner, which could have been accomplished only by one who has spent hours at the bedside and in consultation with active practitioners as well as long hours in the laboratory and library.

The book is divided into three main sections: 1. general principles of pharmacology, in which the history of the subject, details of administration of drugs, relations between pharmacist and physician, etc., are considered; 2. drug action on physiological mechanisms. Here are considered effects on the central nervous system, circulation and kidneys, endocrine and vitamin regulations, the hematopoietic system, and autonomic nervous system, and 3. applications of drugs to clinical medicine. In this section the use of drugs in various disorders of the different body systems is discussed in considerable detail; modern chemotherapeutic agents, including the antibiotics, are reviewed. The book ends with a discussion of elementary clinical toxicology.

It is characteristic of the author that nearly every chapter closes with a section on unsolved problems, in which theories of action are outlined but in which the loopholes in actual proof are pointed out. These sections are most illuminating.

The reviewer salutes Salter's textbook of pharmacology with enthusiasm—for its immense amount of practical information and its scholarly presentation of the fundamentals upon which skillful use of modern drugs depends.

Malaria Terminology: Report of a Drafting Committee Appointed by The World Health Organization. By Sir Gordon Covell, C.I.E., M.D., Paul F. Russell, M.D., M.P.H., and N. H. Swellengrebel, D.Sc. Price, $1.00. Pp. 82, with 8 illustrations. World Health Organization, Palais des Nations, Geneva, 1953.

The preparation of this book by three outstanding malariologists in the world sets forth the terminology used by malariologists in a very detailed manner, which should be accepted by all concerned. Unfortunately for this disease there have been so many different terms utilized by various authors and students of the disease that such a monograph is sorely needed. It is well done and authoritative and is recommended for any student of the disease.

Water, Electrolyte, and Acid-Base Balance: Normal and Pathologic Physiology as a Basis for Therapy. By Harry F. Weisberg, M.D. Price, $5.00. Pp. 245. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1953.

Dr. Weisberg presents this compact volume on fluid and electrolyte balance in the form implied by its subtitle: "Normal and Pathologic Physiology as a Basis for Therapy." The author has written with a clinical point of view. The introductory chapters are devoted to a concise and logical explanation of the normal physiology of body fluids and electrolytes—fluid compartments, endocrine influences, and renal mechanisms. There is a good discussion of acid-base balance. The second section of the book covers the pathologic derangements of the body chemistry. The third section is a discussion of parenteral fluid therapy, in which there is a thorough explanation of types of electrolyte repair solutions and their effective use in states of imbalance. The value of the book is enhanced by the helpful explanatory tables and figures and by the list of 398 references. The book is recommended as a concise and practical review of the subject.

The Ballistocardiogram: A Dynamic Record of the Heart Beat. By John R. Braunstein, M.D., Ph.D. Price, $3.00. Pp. 97, with 64 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1953.

This small monograph, which represents two lectures presented at the University of Cincinnati Medical School, briefly summarizes the history of the development of ballistocardiography. Certain aspects of the characteristics of the normal and abnormal trace are presented, including those for the vectorballistocardiogram. Included is an appendix which describes selected physical phases of the problem. The author implies that the trace has significant clinical applications which exceed the diagnostic usefulness of the electrocardiogram (Fig. 20). The reviewer wonders how well the electrocardiograms were interpreted, for the author suggests the limitations in his knowledge of electrocardiography when he states on page 22 that the H wave begins at approximately "the same time as the intrinsicoid deflection of the electrocardiogram." It is known that the timing of the intrinsicoid deflection of the electrocardiogram within the electrical cycle of the heart varies with the leads. Furthermore, the author has carefully avoided quoting or including data from the medical literature which fail to support his optimistic implication of the clinical significance of ballistocardiography.

These lectures are clearly and succinctly presented. If one is interested in Braunstein's point of view on the subject, he can obtain it from this monograph, even though the author fails to convince the reader of the existence of practical clinical significance of the ballistocardiogram.

Renal Function: Transactions of the Fourth Conference, Oct. 22-24, 1952. Edited by Stanley E. Bradley, M.D. Price, $3.50. Pp. 189. Josiah Macy, Jr., Foundation, 16 W. 46th St., New York 36, 1953.

This discussion on renal function by a multidisciplinary group of experts is devoted largely to the basic physicochemical mechanisms underlying ion exchanges between the fluid compartments of the body, between kidney slices and fluid media, ion transport across surviving frog skin, and movement of water and ions across intestinal epithelium.

While the title of the conference would seem to be only remotely represented in the discussions on the ingenious concepts and experiments on ion transport across various biological membranes, it is obvious that a real comprehension of electrolyte reabsorption and excretion by the kidney will eventually result from such fundamental studies. In this broad sense, renal function is membrane function.

Physicians will be interested primarily in the first chapter, on tissue buffering of acid and alkali and the associated exchanges of hydrogen ion for sodium or potassium, and of chloride for bicarbonate.

Die Zuckerkrankheit: Leitfaden für Studierende und Ärzte. By Prof. Dr. Ferdinand Bertram. Price, d.m. 19.80. Pp. 175, with 25 illustrations and 9 tables. Georg Thieme, Diemershaldenstrasse 47, (14a), Stuttgart-O; American agent Grune & Stratton, Inc., 381 4th Ave., New York 16, 1953.

This is the fourth edition of a modern German textbook on diabetes mellitus, written in an authoritative and well-organized fashion by one of the best informed modern students of the disease in Europe, Professor Bertram, of the university at Hamburg. There is good coverage of basic mechanisms, pathogenesis, behavior, and treatment of the disease in adults and children.

In its organization and thoroughness this material is reminiscent of those fine early source books on diabetes written by Naunyn and von Noorden.

Mechanisms of Urologic Disease. By David M. Davis, M.D., Professor of Urology Emeritus, Jefferson Medical College; Visiting Lecturer in Urology, Graduate School of Medicine, University of Pennsylvania. Price, $4.50. Pp. 156. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1953.

This small volume is a syllabus intended for third year medical students and serves this purpose only. Essentially, it introduces urology on the physiologic and pathologic instead of the anatomic basis. Eight types of change are emphasized throughout as the basic elements of the

mosaic of urologic diseases—obstruction, infection, lithiasis, neoplasm, congenital malformation, trauma, foreign body, and neurogenic changes. Each of these is considered with appropriate illustrations from specific diseases. The discussion is terse, concentrated, and to the point. The chapters on catheterization and history taking and physical examination are useful. There is a list of recommended reference books, including the standard American texts. It is to be regretted that the author did not expand this book into a more complete discussion of urologic mechanisms, suitable for the general physician.

Fibrocystic Disease Of The Pancreas. By Martin Bodian, M.D. Price, $9.50. Pp. 244, with 133 figures. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1953.

This monograph is a collection and detailed survey of cases of fibrocystic disease of the pancreas seen at The Hospital for Sick Children, in London. An account of the literature is presented which is clear and concise. A chapter on clinical material conveys the over-all features of 116 case reports, to include the natural history of fibrocystic disease of the pancreas; various laboratory investigations, such as pancreatic enzyme determinations and roentgenologic data, and the treatment of the disease. There is an outstanding chapter on the familial incidence of the disease, in which 77 family trees are studied. The chapter on pathology is detailed and is abundant with gross photographs and photomicrographs. The main concept is that fibrocystic disease of the pancreas is the result of "mucosis," a fundamental abnormality of mucous secretion of epithelial cells wherever in the body mucus is secreted. Hence, there are found histologic lesions in the intestinal tract, salivary glands, pancreas, liver and biliary tract, and the entire respiratory tract, including the nasopharynx. There is a chapter which illustrates the salient clinical points and autopsy findings in 116 cases of this disease, unmarred by superfluous details. Lastly, there is a discussion of two congenital pancreatic dysplasias, namely congenital hypoplasia of the exocrine pancreas and congenital cystosis of the pancreas. This edition represents the outstanding publication on this subject, which every pediatrician or gastroenterologist should read.

The Ciba Collection Of Medical Illustrations: Volume 1; Nervous System. By Frank H. Netter, M.D. Price, $6.00. Pp. 143, with 104 illustrations. Ciba Pharmaceutical Products, Inc., 556 Morris Ave., Summit, N. J., 1953.

This large cloth-bound collection of illustrations of anatomic and pathologic conditions of the spine and central nervous system is another excellent contribution of the physician-artist Frank H. Netter. It is a companion volume to the first "Ciba Collection of Medical Illustrations," published in 1948. The text and colored pictures are divided into five main sections: 1. Anatomy of the Spine, 2. The Central Nervous System, 3. Functional Neuroanatomy, 4. The Autonomic Nervous System, and 5. Pathology of the Brain and Spinal Cord. Though the approach is mainly anatomic, of singular interest is the outstanding section dealing with functional neuroanatomy, where vivid illustrations of a highly complex subject are adequately presented. Similarly, the chapter on the autonomic nervous system is very clearly portrayed in a manner in which both morphology and its relation to function are presented. The artistry of this volume is coupled with authoritative though concise explanatory texts. If the object of the book is to present to the physician an accurate and uncomplicated pictorial and graphic review of the nervous system, this is well achieved. Its information can be grasped by the medical student and the neurologic practitioner alike, to whom it is recommended.

Atlas of Medical Mycology. By Emma Sadler Moss, M.D., and Albert Louis McQuown, M.D. Price, $8.00. Pp. 245, with 248 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1953.

This is a book for which there has long been a real need. All the fungus diseases encountered in this country are classified and briefly described. Along with the clinical description, which admittedly is sketchy, the technique of discovering the organisms in the lesions in question is given in adequate detail. These descriptions, usually covering no more than three or four pages of printed material, are accompanied by an equal amount of space allotted to illustrations of the gross lesions, x-ray appearance, appearance of the colonies on culture media, and microscopic preparations made directly from lesions and from cultures. The chapters on methods

of obtaining material and examining it, preparation of culture media, etc. are short and practical. The authors have found Littman oxgall agar often more useful than Sabouraud's agar as an identifying medium.

The book is printed in very readable type, and the illustrations are excellent. The reviewer has no reluctance in recommending the book enthusiastically to all persons interested in infectious diseases.

Studies on Mouse Encephalomyelitis Virus: TO Strain; Observations on the Oral Route of Infection and on the Epidemiology of the Disease. By Herdis von Magnus. Price, not given. Pp. 20. Kobenhavns Universitet, 1952.

The TO strain of mouse encephalomyelitis virus is the original strain of an agent isolated by Theiler from a spontaneous disease in mice. The agent has been used for much laboratory investigation related to poliomyelitis since there are many similarities between the Theiler virus and the agent of poliomyelitis.

Herdis von Magnus, in her paper, reports on a series of interesting studies on the epidemiology of this disease in the natural host.

Propagation of the PR 8 Strain of Influenza A Virus in Chick Embryos: Studies on the Factors Involved in the Formation of Incomplete Virus upon Serial Passage of Undiluted Virus. By Herdis von Magnus. Price, not given. Pp. 32. Kobenhavns Universitet, 1952.

Previous studies on the multiplication of PR 8 influenza virus have shown that under certain conditions an incomplete virus was formed. It was detected by the fact that it will react with specific antiserum, but it will not produce infection in chick embryos or mice.

In this investigation, Preben von Magnus makes a thorough study of some of the factors (such as concentration of inoculum, length of incubation period, and site of inoculation in chick embryos) on the production of the incomplete virus.

This is an excellent piece of work, but it is of greatest interest to the virologist and not to the practicing physician.

Surgical Forum, 1952: Clinical Congress of the American College of Surgeons. By many authors. Price, $10.00. Pp. 716, with 314 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1953.

"Surgical Forum" consists of a compilation of the papers presented at the Clinical Congress of the American College of Surgeons. This meeting deals with the results of original research on fundamental problems of pathologic physiology, as related to surgery. Correlation with clinical material is included in many of the papers. The material covers a wide field of surgical interest. Included are sections on stomach, esophagus, intestine, portal hypertension, thermal injuries, and surgery of the heart and great vessels. Basic problems related to water balance, electrolytes, anesthesia, shock, and infection are included. This volume affords excellent browsing for both internist and surgeon alike.

The Surgery of Infancy and Childhood: Its Principles and Techniques. By Robert E. Gross, M.D., D.Sc. Price, $16.00. Pp. 1,000, with 1,488 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1953.

"The Surgery of Infancy and Childhood," by Robert E. Gross, should be read and studied by all pediatricians, general practitioners, and surgeons. The essentials in embryology, etiology, and clinical findings in this age group are most interestingly presented, with many diagrams, x-ray reproductions, and photographs of patients and pathological specimens, so that each subject is superbly presented. Methods of treatment are well discussed, and the tremendous clinical experiences are well edited and tabulated so as to indicate clearly to the reader the preferred methods of treatment. The descriptions and illustrations of surgical techniques used are unexcelled. There are 64 chapters, delving into practically all surgical problems of the

premature infant, the infant, and the child (neurosurgery, orthopedic, and ear, nose, and throat surgery excluded). The chapter concerning preoperative and postoperative care should be a stimulus and guide to all pediatric surgical services. The common surgical problems of childhood are not neglected for the rare or unusual. The book contains the latest developments in surgery, methods of diagnosis, and treatment. It is written so that it is stimulating and a pleasure to read.

Diuretic Therapy: The Pharmacology of Diuretic Agents and the Clinical Management of the Edematous Patient. By Alfred Vogl, M.D. Price, $5.00. Pp. 249. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1953.

This book covers the entire subject of diuretics and their use in an exemplary manner and will fill a long felt need. There is a systematic discussion of the mechanisms of edema of various types, the pharmacology of diuretic drugs as well as the antidiuretic agents, the clinical details of diuretic management, and the various complications and side reactions of excessive diuresis. Throughout there are appropriate historical comments, correlation between physiological and clinical facts, and a large amount of interesting and useful information.

The style is clear and direct; dogmatism is avoided; areas that require further investigation are pointed out. The bibliography is excellent, comprising 725 carefully selected references.

This book will undoubtedly become a classic and should prove of much value to practicing physicians, medical students, and investigators interested in the physiology of edema and diuresis. It is fitting that the author was the first to observe the remarkable diuretic effect of an organic mercurial compound.

The Diabetic Neuropathies. By Joseph I. Goodman, and others. Price, $4.75. Pp. 138, with 6 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1953.

This monograph presents the results of a group study on 162 cases of diabetic neuropathy among 261 diabetic patients. The material is well arranged and gives a brief but excellent description of symptomatology, clinical types, theories of pathogenesis, pathology, course and prognosis, differential diagnosis, and treatment. There are a good summary, an excellent bibliography, and index. The format is attractive.

As to pathogenesis, the various theories are reviewed—arteriosclerosis, vitamin or other dietary deficiency, unknown intermediate metabolites with toxic action on nerves, etc. The last is given preference because of the relationship of neuropathy to poor control of diabetes and malnutrition. Ischemic neuropathy was rarely found.

Treatment emphasizes adequate control of diabetes and the usual symptomatic measures.

While there is nothing original in this volume, it is an excellent review of the subject.

Epidemiology and Control of Endemic Syphilis: Report on a Mass-Treatment Campaign in Bosnia. By E. I. Grin, M.D. Price, $1.00. Pp. 93. Columbia University Press, 1952.

This publication represents a monographic presentation of material previously published in the *Bulletin of the World Health Organization* (**7**:1-74; 75-81, 1952). It includes studies, in Bosnia, Yugoslavia, on the natural history and control of endemic syphilis, a treponemal disease of childhood. In addition there are detailed investigations by Turner and Hollander on treponemes isolated from patients with this endemic syphilis. The important principles emphasized are that successful control efforts must include systematic examination of the entire population, that the clinical features of endemic syphilis are essentially similar to those of sporadic syphilis, and that the organism causing the endemic infections belongs to the general group of strains designated as Treponema pallidum. The reader will find the organization of the field campaign carefully outlined, as well as the method of mass therapy used. It is possible under favorable circumstances to eliminate the reservoirs of infection in a short time. This campaign, so well described by Grin, is another of the great projects fostered by the World Health Organization. Some of this information and results accomplished by this means will undoubtedly prove useful in the eradication of certain endemic diseases in some of the less medically developed areas in the United States.

Therapeutics in Internal Medicine. Edited by Franklin A. Kyser. Second edition. Price, $15.00. Pp. 830. Harper & Brothers, 49 E. 33rd St., New York 16, 1953.

Very little can be said of this volume except praise. Consisting of 18 chapters written by 84 authorities and devoted to the treatment of specific diseases, with one chapter in which symptoms are made the basis of treatment, the field of internal medicine is well covered. An appendix of 22 pages relating to useful diets would certainly be regarded as inadequate for this type of therapy by many dietetic enthusiasts, but to the reviewer it appeared that all really useful diets were adequately represented. Other special methods of treatment, for example physical medicine, are represented only by incorporation into the body of the discussion of the specific diseases. This appears adequate for a book of this type. The discussion on psychosomatic problems is an especially good down-to-earth exposition, free from the usual pseudoscientific camouflage. This text is recommended without reserve to the general practitioner, for whom it obviously was largely designed.

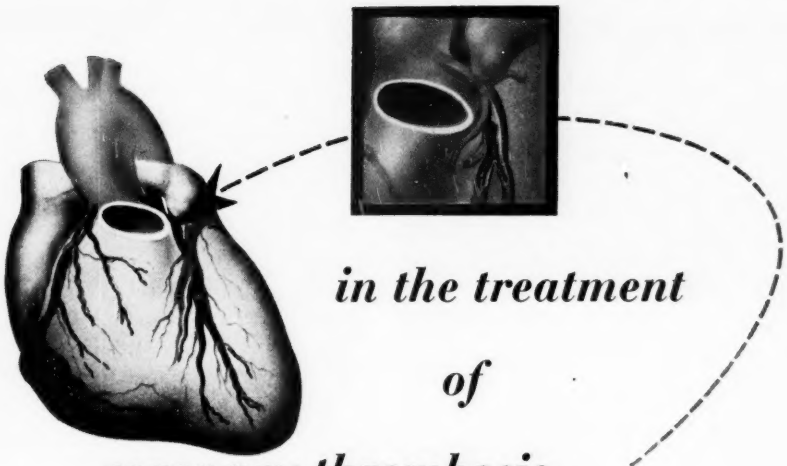
First International Symposium on Yaws Control. Price, $4.50. Pp. 418. World Health Organization, Palais des Nations, Geneva, Switzerland, 1953.

This bulletin is of value to those interested in the problem of yaws, and is an important reference on the subject.

Surgery of the Pancreas. By Richard B. Cattell, M.D., and Kenneth W. Warren, M.D. Price, $10.00. Pp. 374, with 100 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1953.

Cattell and Warren have made a valuable contribution in "Surgery of the Pancreas," a book of 374 pages, which contains 100 illustrations and numerous tables. In their enlightening and essentially practical treatise on surgical lesions of the pancreas the authors present not only their large personal experience and opinions but also the accumulated experience of the Lahey Clinic. Since the book apparently is designed primarily for the practicing clinical surgeon, much detail which might appear in a book prepared especially for the undergraduates is omitted. As a result, the presentation is concise and direct and the practical clinical and surgical considerations are easily accessible to the reader. Anatomy and physiology of the pancreas are reviewed, but the major portion of the book is devoted to diagnosis, clinical management, surgical indications, and treatment of the most important lesions of the pancreas which are of interest to the surgeon. Less common pancreatic lesions such as annular pancreas, pancreatic injuries, and complications of pancreatitis are also discussed, and their management is described.

Acute and chronic relapsing pancreatitis, hyperinsulinism, and carcinoma of the head of the pancreas and periampullary region are discussed from the viewpoint of diagnosis, clinical management, surgical treatment, and results. These subjects, as others in the book, are presented in a clear and lucid manner. The liberal use of individual case histories serves to emphasize points of clinical and surgical significance. The authors' views and recommendations on currently controversial subjects, such as the treatment of pseudocysts of the pancreas, methods of establishing drainage from the pancreas into the intestinal tract after resection of the head of the gland, surgical indications in chronic relapsing pancreatitis, and similar subjects, are clearly given. The prevention and treatment of pancreatic injuries, particularly injuries of the pancreatic ducts such as may occur in certain operations on the stomach and duodenum, are discussed in an enlightening and practical manner. Technical aspects of the Whipple operation are discussed in some detail. Most other surgical procedures are reviewed in a somewhat more general manner. The wide personal experience of the authors, which they have drawn on so liberally, makes this book a valuable reference on surgical indications, procedures of treatment, and results. The bibliography includes many worthwhile references.



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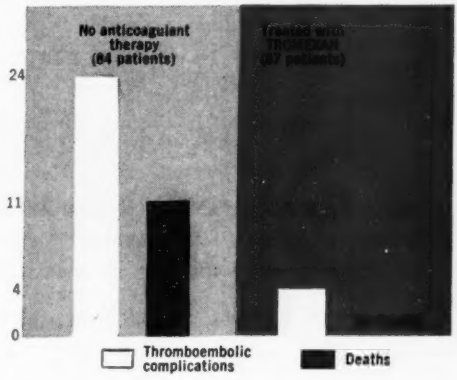

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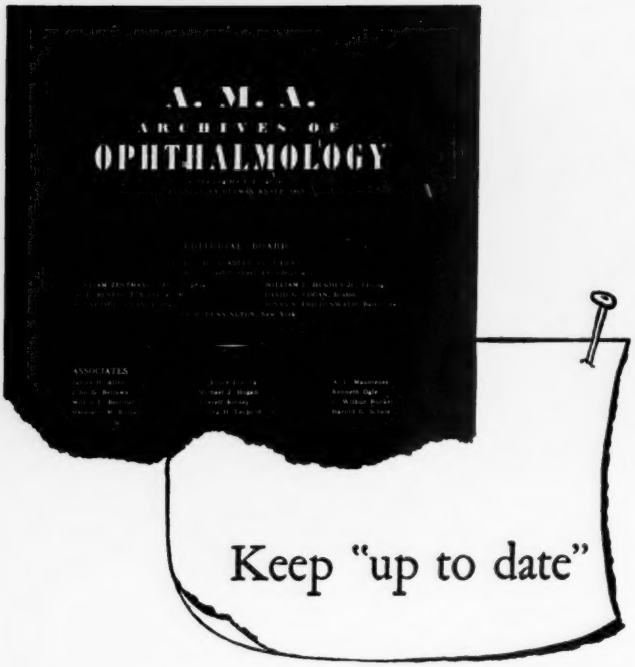

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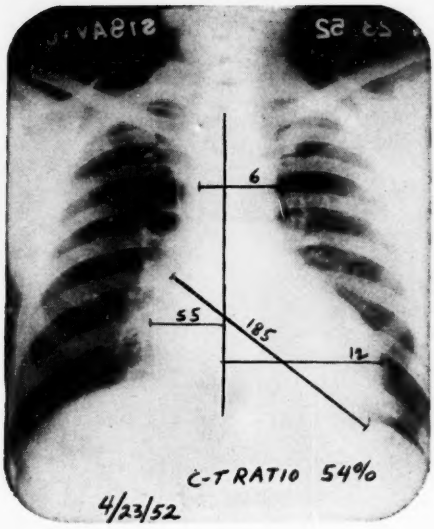
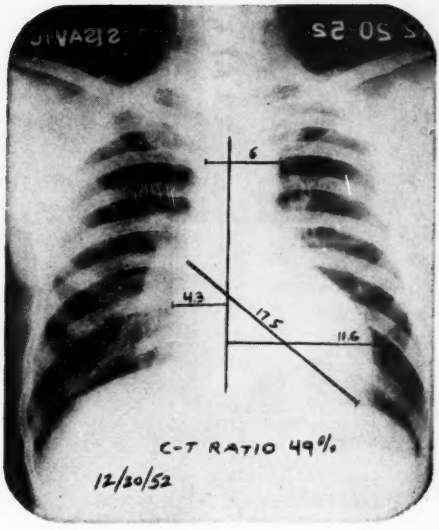


Patient F.S. before Methium: Cardio-thoracic ratio 54%, blood pressure 240/160 mm. Hg.[1]



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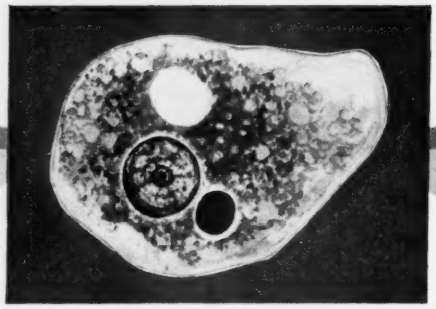

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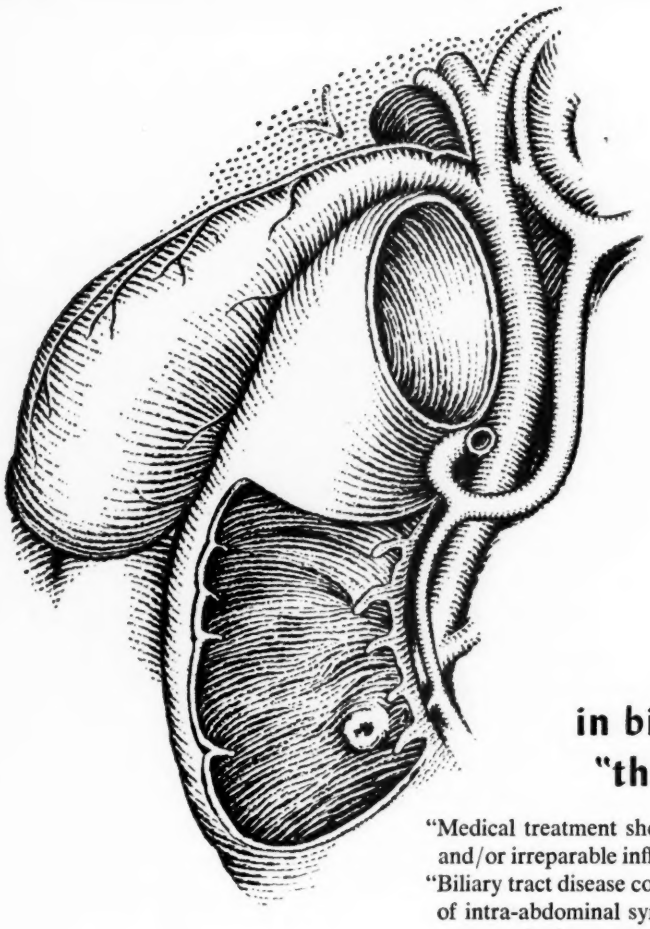

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